CRANFIELD UNIVERSITY

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THE USE OF QUANTITATIVE ULTRASOUND ON THE FINGER TO DETECT OSTEOPOROSIS

DEFENCE COLLEGE OF MANAGEMENT AND TECHNOLOGY

PhD
Abstract

The current demand on densitometry services has led to many patients at risk waiting long periods of time, while other healthy individuals are scanned unnecessarily. This work sets out to address the issue of pre-screening for DXA in a postmenopausal population. With simple pen and paper assessments possible, the most important risk factors were selected based on comparison with actual DXA T-Scores. This enabled the creation of a very simple tool that may aid with the prioritisation of those most in need of investigation.

The success of commercial QUS devices prompted the inclusion of a number of ultrasound measurements. When added to the simple tools the performance markedly improved. Other known QUS parameters used at the proximal phalanx demonstrated very weak links, if any, with DXA measurements suggesting they may not be useful when it comes to screening large numbers of people. Energy measurements of the phalanx were shown to be correlated to cortical thickness. As cortical thinning is known to advance as osteoporosis worsens, these measurements are proposed as a method of predicting those with low bone mineral density. Further examination found that the thickness was related to density at the neck of femur. This strengthens the claim that energy measurements may accurately choose those requiring immediate intervention.
Acknowledgements

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The CT machinery and expertise that was needed was provided by Keith in Manchester and Bert and Lars in The Netherlands.

Finally I would like to thank my friends and family who have put up with me and kept my spirits up for so long. The greatest thanks go to my parents, Carthy and Tony. They have help me along my path for a quarter of a century now, they are the best parents I could ever have hoped for.
Contributions to Knowledge

- Formulation and validation of a risk factor based assessment tool for predicting osteoporosis in postmenopausal, British women.

- The addition of QUS measurements to known risk factors to increase the sensitivity and specificity of assessment tools.

- Comparison of proposed and novel ultrasound parameters at the finger with density at the axial skeleton.

- Development of a method for predicting morphology of the proximal phalanx \textit{in vivo} using ultrasound techniques.

- Investigation of the relationship between the morphology of the proximal phalanx and the density of the neck of the femur.
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Glossary

$\mu$CT  Micro Computed Tomography
AUC  Area Under the Curve
BMC  Bone Mineral Content
BMD  Bone Mineral Density
BMU  Bone Modelling Unit
BRU  Bone Remodelling Unit
CCT  Combined Cortical bone Thickness
CT  Computed Tomography
CV  Coefficient of Variation
BUA  Broadband Ultrasound Attenuation
DPA  Dual Photon Absorptiometry
DXA  Dual energy X-ray Absorptiometry
FN  False Negative
FP  False Positive
HRT  Hormone Replacement Therapy
LSC  Least Significant Change
MCI  Metacarpal Index

MTI  Monitoring Time Interval

NOF  National Osteoporosis Foundation

NTF  Non Traumatic Fracture

NPV  Negative Predictive Value

ORACLE  Osteoporosis Risk Assessment by Composite Linear Estimate

OSIRIS  Osteoporosis Index of Risk

OST  Osteoporosis Self-assessment Tool

PPV  Positive Predictive Value

pQCT  Peripheral Quantitative Computed Tomography

PRO  Proportion of energy arriving from the cortical bone

QUS  Quantitative Ultrasound

ROC Curve  Receiver Operating Characteristic Curve

SCORE  Simple Calculated Osteoporosis Risk Estimation

Sensitivity  The measure of the ability of a test to correctly select those with a disease

SI  Stiffness Index

SOS  Speed Of Sound

SPA  Single Photon Absorptiometry

Specificity  The measure of the ability of a test to correctly select healthy individuals

T-score  BMD compared to young, healthy population

TAI  Trend Assessment Interval

TAM  Trend Assessment Margin

TN  True Negative
TP  True Positive

TOF  Time of Flight

UBPI  Ultrasound Bone Profile Index

SPA  Single Photon Absorptiometry

SXA  Single energy X-ray Absorptiometry

VOS  Velocity Of Sound

WHO  World Health Organisation

Z-score  BMD compared to age matched population
Chapter 1

Introduction

*Old age is, so to speak, the sanctuary of ills; they all take refuge in it*

Antiphanes

Hubert Humphrey remarked 'It was once said that the moral test of government is how that government treats those who are in the dawn of life, the children; those who are in the twilight of life, the elderly; and those who are in the shadows of life, the sick, the needy and the handicapped'. It is with this virtue foremost in mind that the work presented here attempts to alleviate, at least in some part, current issues which directly affect the daily lives of many elderly members of society. It deals with the detection of osteoporosis, a condition that if left untreated may result in an unexpected fracture and reduced mobility. However, with early diagnosis and the appropriate treatment, the probability of suffering an osteoporotic fracture is reduced. It is therefore imperative to strive to preserve the quality of life for as many older people as possible.

Osteoporosis has affected people for as long as evidence exists. It has been suggested that osteoporosis caused fractures in the vertebral bodies of skeletons thousands of years
old, which would have resulted in immobility in later life [Teschner, 2007]. However, the
disease was discovered much more recently. Firstly came the theory of bone remodelling
put forward by Dr. John Hunter who observed that bone growth depended on resorption
and deposition. This provided a better understanding of bone, as a living tissue, and a
platform for future research. The coining of the term osteoporosis is often credited to
Jean Georges Lobstein who observed that some bones contained holes that were larger
than normal. Astley Cooper also made a significant contribution to the field, detailing
many of the fractures which result from decreases in bone content. He also observed
the deterioration of bone with age, noting that cortical bone thinned and spongy bone
could be marked using a penknife, which was not possible in bones of younger adults
[Cooper, 1851]. The next milestone was made by Fuller Albright who proposed the link
with menopause. Finally, from the mid-point of the last century accurate and precise
methods of measuring bone mineral density were developed. This enabled the in-vivo
determination of density, which has been used as a marker for bone resorption ever since.

Owing to large amounts of research, much more is now known about osteoporosis and
how it affects the human body. It is a systemic condition which leads to reductions in the
thickness of cortical bone and the number and thickness of trabeculae in cancellous bone
[Seeman, 2003b]. These changes result in lower bone mass for those affected. The two
dimensional nature of original absorptiometry techniques allowed for the calculation of
areal bone density. This is the measured bone mineral integrated for the scanned area. As
these measurements reflect the changes in mineral content they became the gold standard
for assessing skeletal condition. In an attempt to tie absorptiometric results to fracture
risk, a WHO study group suggested comparison with BMD or BMC of the ‘young healthy
adult’. Any score greater than -1 SD of the young healthy mean represents normal, between -1 SD and -2.5 SD is osteopenic and less than -2.5 SD is osteoporotic [Alexeeva et al., 1994]. A score less than -2.5 SD accompanied by a fragility fracture is considered severe osteoporosis.

The resorption of cancellous bone and thinning of cortices culminate in an increased risk of fracture, even for low energy impact. The major morbidity is fracture at the hip, vertebral spine and wrist, all of which are comprised of both types of bone. The problem facing the current health services is immense, the magnitude of which is probably best demonstrated by the number of fractures that occur. Predictions made using data from England and Wales suggest that the lifetime risk of fracture for females at the age of 50 is 53.2%, while for males at the same age the risk of fracture is 20.7% [Van Staa et al., 2001]. While fracture itself may be debilitating and cause distress for an individual, there also exists secondary consequences. These include reduced mobility and possible mortality associated with surgery. For example, exaggerated curvature of the spine and reduced mobility, both of which may result from fracture of one or more vertebral bodies, have been shown to be significantly correlated to reduced quality of life [Miyakoshi et al., 2003]. More worryingly perhaps, are figures for the UK which show that rates of mortality following neck of femur fracture may be as high as 18% three months postoperatively [Todd et al., 1995].

While the direct outcomes of osteoporosis are obviously endured by the individual, there is also a substantial cost to the government. In terms of monetary value, the cost of hip fractures in the UK has been estimated at almost £726 million [Anonymouse, 2000]. However, many more pessimistic approximations have been put forward. Treatment also
places a heavy burden on hospitals, ambulance services, social care and general practitioners. Women recovering from osteoporotic fracture require significantly more GP visits (almost 14 in the case of vertebral fracture) and outpatient referrals (28 orthopaedic referrals in the case of hip fracture), compared with controls [Dolan and Togerson, 1998]. It is also estimated that 20% of all orthopedic beds are occupied by those affected by hip fracture [Kanis and McCloskey, 1998].

In light of the fact that changes in skeletal condition can be detected, and that drug treatments have been shown to reduce the risk of fracture at the hip, vertebra and wrist [Reginster et al., 2005, Ettinger et al., 1999], a prophylactic approach stands out as the most appropriate means of tackling the issue. This offers the opportunity to protect those at highest risk and to reduce the costs involved with treating fractures. This has focussed the attention of many to the earlier detection of deleterious changes in bone quality.

One of the first means of diagnosing osteoporosis, radiogrammetry, relied on measuring cortical thickness of metacarpals from X-ray films [Barnett and Nordin, 1960]. This enabled clinicians to quantify the loss in bone mass. Possibly the largest limitation to this type of evaluation is the fact that details of the structure of the cortical bone are ignored; porosity and resorption on the endocortical surface.

Radiogrammetry was superseded by Radiographic Absorptiometry (RA). Single Photon Absorptiometry (SPA), the original technique introduced by Cameron and Sorenson [1963] used a single \( \gamma \)-ray source to measure the photons that cross the site of interest. The attenuation of the beam is dependent on the amount of mineral present, and was therefore used to calculate the BMC, or BMD based on the known dimensions of the bone. SPA requires the site of interest to be surrounded by tissue equivalent material, water,
which limits its use to the peripheral skeleton. The use of a second source of $\gamma$ radiation of a different energy level, Dual Photon Absorptiometry (DPA), meant that the soft tissue could be corrected for, negating the need for a water bath. Measurements at the clinically relevant axial skeleton could now be carried out.

The principles of Single energy X-ray Absorptiometry (SXA) and Dual energy X-ray Absorptiometry (DXA) are similar to those for SPA and DPA, except that X-rays replace $\gamma$-rays. DXA at the hip and lumbar spine is currently the gold standard absorptiometric approach, with precision values of 0.5–2.0% for the lumbar spine and 1–5% for the proximal femur [Adams, 1997]. The use of areal density of the axial skeleton as a means of determining fracture risk may indeed be appropriate. For instance, changes in BMD may indicate the same increase in risk of fracture as high diastolic blood pressure at predicting stroke, or cholesterol or smoking at predicting coronary heart disease [Marshall et al., 1996].

While BMD may give some indication as to the risk of subsequent fragility fracture, is a simple measure of bone mass the best method of gauge the progress of osteoporosis? No account is taken of the state of the bone that is investigated. DXA cannot provide information about the continuity or thickness of the trabeculae within the region of interest. The same can be said of the Young’s modulus, one of the most important factors in determining the strength of a material. Another potential source of error is the over estimation of BMD that results from osteoarthritis. The increased mineralisation present at the articulating surface may mask the decreased bone mineral content in cancellous bone. This has been linked with the misdiagnosis of osteoporotic individuals as osteopenic [Liu et al., 1997]. Kanis [2002] has suggested that indeed BMD may not be appropriate for the diagnosis of
osteoporosis. Other risk factors exist, and only when these are evaluated with BMD can the most accurate categorisation of risk be carried out.

Quantitative Ultrasound (QUS) has been proposed as an alternative means of predicting fracture risk. As sound waves propagate, they are altered by the material properties and the structure of medium through which they are travelling. Speed of Sound (SOS) was the first ultrasonic parameter to be studied clinically. SOS measurements are mostly performed at the appendicular skeleton, where little soft tissue covers the bone surface. The SOS values are related to the density [Knapp et al., 2001] and the Young’s modulus [Muller et al., 2008] of the bone. As a result, good correlations have been observed between SOS and BMD, both close to measurement site [Louis et al., 1998] and at the axial skeleton [Benitez et al., 2000].

Langton et al. [1984] proposed the use of Broadband Ultrasonic Attenuation (BUA) across the calcaneus as a means of measuring bone quality. This involved performing a fast Fourier transform on the waveform that crosses the heel. For better quality bone, higher frequencies are more acutely attenuated. BUA is generally considered to depend on the density [Rho et al., 1997] and the structure of the bone [Hans et al., 1995]. Many researchers have found good agreement between BUA and BMD at the hip and spine [Kovac et al., 2003, Cook et al., 2005]. It is proposed that this agreement stems from the fact that the heel bone is mostly the metabolically active cancellous bone, where changes in bone quality will be observable sooner, and that the heel undergoes similar stress cycling as the hip and spine.

Many other QUS parameters have been studied as predictors of density, or in terms of changes with age, with varying degrees of success. Wüster et al. [2000] found 'Fast
Wave Amplitude’, ‘Signal Dynamics’, ‘Time Frame’ between the first and last amplitude and overall ‘Signal Amplitude’ all decreased with age from the fourth decade. Using a combination of the signal dynamics, fast wave amplitude and the time frame they created the Ultrasound Bone Profile Index (UBPI). UBPI showed a greater correlation with BMD at the lumbar spine and hip than SOS at the same site. Another commonly used variable is Stiffness Index (SI). This is composite value based on BUA and SOS across the calcaneus and not to be confused with mechanical stiffness.

Not only has QUS shown good correlation with BMD, it has also been shown to be effective at predicting fracture risk. Measurements from the heel [Njeh et al., 2000], radius [Hans et al., 1999a] and finger [Mussolino et al., 1997, Reginster et al., 1998, Guglielmi et al., 1999] have shown promising ability, even when compared to BMD measurements, with regard to selecting those with an osteoporotic fracture. Furthermore, it has been shown that risk of fracture for the hip based on QUS at the heel remains significant even when BMD at the hip was accounted for [Hans et al., 1996]. Similarly, ultrasound was shown to be related to the mechanical properties, even when adjusted for density [Rho et al., 1997]. This supports the theory that QUS may provide important information about the quality of bone, independent of the density.

This work sets out to investigate the most significant risk factors for osteoporosis in a British population. In addition, given that the International Quantitative Ultrasound Consensus Group advocate the use of QUS for diagnosing osteoporosis, predicting fracture risk and monitoring skeletal changes [Glüer, 1997], certain ultrasound measurements will also be included as possible independent variables. Currently, reductions in bone mass are determined via DXA analysis of the hip and spine. The reductions in bone mass are used
to explain the decrease in mechanical competency of bone, which in turn is used to predict
the risk of fracture for an individual (Figure 1.1). It is proposed that QUS may provide a
simple screening tool for osteoporosis by determining the mechanical competency of the
skeleton. This raises the question whether or not QUS should be used independently of
DXA scanning. Indeed, Gregg et al. [1997] have suggested that QUS be used in combi-
nation with BMD because they are independent predictors of fracture risk. While ideally
it may be better to consider the results of both techniques, for the purposes of this work,
it was assumed that in certain cases only QUS may be available. Indeed, this is accepted
as a viable means of pre DXA scanning [Gambacciani et al., 2004]. Although, as DXA
results remain the clinically accepted gold standard, it is still necessary to compare the
results of all new techniques for predicting osteoporosis, including those presented here,
with densitometric T-scores.

The goals of this project are twofold: determine the most influential predictors of risk
factors for a British population and optimise the use of ultrasound as a means of ascertaining
bone quality. As such, it seems logical to divide the methodologies into two distinct
paths. The first of these would be to collect patient data, via questionnaires, for those
whose DXA T-score are known. This would permit the use of regression analysis to find
the risk factors which have the greatest influence on the BMD. In parallel with this study,
it is essential to document the correlation between DXA T-scores and currently available
QUS devices to ensure that the use of questionnaire analysis is not made obsolete by more
predictive ultrasound methods. The second part of the research deals with the optimisation
of ultrasound techniques for the same population. In order to achieve this, it is necessary
to design and manufacture a prototype device capable of scanning a region of interest
Chapter 1. Introduction

Osteoporosis

Increased Fracture Risk

Reduced Bone Mechanical Competency

Reduced Bone Mass

Reduced DXA T-score

Reduced QUS Result

Figure 1.1: Osteoporosis and the associated phenomena. Currently, reductions in bone mass are detected using DXA T-scores (Dashed Line). These are assumed to reflect the decreases in mechanical competency and the increase in the likelihood of fracture (Dashed Line). QUS may be useful for monitoring changes in risk of fracture as it has been shown that QUS results are correlated to the mechanical competency and reduced mass of the bone. Solid lines indicate previously investigated relationships.

demed relevant. Whatever the manifestation of osteoporosis that is being monitored, it is required that this be clearly analysed with respect to the ultrasound parameter. Therefore, all experimentation using the prototype ultrasound device will be compared to CT data from the same site. In order to be accepted by the densitometry community, comparison to BMD values at clinically relevant sites is also of paramount concern. Therefore, where possible, this will also be carried out.

The main deliverables of this research should aid with the prioritisation of those at highest risk of suffering an osteoporotic fracture. The simplest and most straightforward
product of this research would be an assessment tool capable of categorising people based on risk of osteoporosis. This could help in areas where current facilities are under severe pressure by selecting only those most in need of attention. As current QUS devices will also be studied, this will allow for a more accurate assessment procedure. This may be of benefit where QUS services are already available. QUS and risk factor analysis could also prove exceptionally useful if adopted by general practitioners and point of contact health care professionals. Ideally, these services would be offered as part of routine checkups, which could allow for the earlier detection of bone mass loss which are currently left unchecked in many cases. The final stream, the development of a prototype scanning system, has the potential to allow earlier, more appropriate, diagnosis of systemic changes in the skeleton.

In conclusion, the end point of this work is to summarise the current early warning systems for osteoporosis with a view to improving their accuracy and usefulness. The potential benefits are enormous to both to the individual, where one may avoid a serious fragility fracture, and to the government, by reducing the cost of treating such fractures.
Chapter 2

Literature Review

_The only good is knowledge and the only evil is ignorance_

Socrates

In order to investigate the detection of osteoporosis it is important first to understand how healthy bone behaves and functions. This chapter briefly introduces the idea of bone as a material, describing the composition, structure and how it is created. The process of bone loss and the changes associated with osteoporosis are then presented. Finally, the way in which current diagnostic techniques operate and the method of assessing how new tests are evaluated.

2.1 Bone

To truly understand the problem of osteoporosis and its detection, one must first understand the function, composition and structure of bone itself. Also, the way in which bone regenerates is important as it may explain how bone is lost later in life. This section describes healthy bone.
2.1 Bone

2.1.1 Function

Bone, either as a single unit or as part of the skeletal system, performs a number of tasks. By working together, bones allow for articulation by providing sites for muscle attachment and acting as levers to allow muscular contractions to flex or extend joints. The skeletal system also protects the vital organs and delicate bodily systems, essential for survival, by surrounding them. The other major function of bone is to act as a reservoir for many key ions such as calcium, phosphorus and magnesium. Besides all this, many bones are hollow structures which are filled with marrow, which produces required blood cells.

2.1.2 Structure

The all encompassing term bone tends to give the illusion that all bone is a simple, continuous material. However, one must look at it as a hierarchical structure. Figure 2.1 demonstrates this perfectly. On the smallest scale, it shows the arrangement of the collagen and the bone crystals. Repeating sequences of these are the building blocks for collagen fibrils, which are grouped to form collagen fibres. Many of these fibres are then arranged in parallel to create lamellae. Osteons are made up of concentric sheets of these lamellae, however the collagen fibres in each layer are not parallel with fibres of consecutive layers.

2.1.3 Macrostructure

The previous section describes how collagen and mineral are arranged, on the microscopic level, to form lamellae and osteons. The next step on the hierarchical ladder is the macrostructure, where bone is either cortical or cancellous in structure, the main differ-
Figure 2.1: The hierarchical structure of bone is evident from this depiction. The organisation of successive levels, from collagen and mineral up to the osteon, is also clearly presented. Reproduced with permission from Rho et al. [1998].

ence being the higher porosity of the cancellous bone. A threshold of 70% volume fraction is used, with any values greater denoting cortical bone and values less denoting cancellous bone [Carter and Spengler, 1978]. The apparent density of cortical bone is approximately 1.64 g.cm$^{-3}$ at the femur and 1.54 g.cm$^{-3}$ at the tibia [Yeni et al., 1998]. These are significantly greater than apparent densities of cancellous bone which is 0.47 g.cm$^{-3}$ at the femur [Li and Aspden, 1997] and 0.22 g.cm$^{-3}$ at the lumbar spine[Cendre et al., 1999]. Both of these types of bone are visible to the naked eye. Figure 2.2 shows examples of these.

Figure 2.2: Cross section of a vertebral body. The cortical bone is present as a solid shell. The cancellous bone is present in the spongy centre of the vertebral body.
2.1. Bone

Cortical Bone

Cortical (or compact) bone is the most common type of bone, making up 80% of the skeletal system. It may be considered solid, however some voids exist. These may be present as canaliculi and erosion cavities or as cavities filled with osteocytes or blood vessels. The porosity of this type of bone is in the range of 3.2–6.1% for healthy young adults [McCalden et al., 1993]. However this can be greater, 7%, for older or osteoporotic subjects [Roschger et al., 2001]. In this case, porosity was calculated from small sections of cortical bone from within the cortex. Even greater values can be measured if trabecularisation of the endocortical surface is included, ranging from 4.6–35.6% [Bayraktar et al., 2004]. The solid, stiff nature of cortical bone makes it an ideal material for the shafts of long bones, allowing the transfer of load between joints and ensuring that muscle contractions move bones that hold their shape. It is also found covering the ends of long bones, forming a shell around shorter bones and acting as the outer layers in sandwich bone.

Cancellous Bone

Cancellous (or trabecular) bone makes up remaining 20% of bone present. Cancellous bone can be described as a tortuous network of plates and rods, roughly oriented along the major axis of applied force. It is present at the end of long bones, in the central cavity of short bones, in the vertebral bodies and often filling the gap between sheets of cortical bone in sandwich bone. It is typically present where loads are distributed over large areas, where solid cortical bone would make for over-engineering and unnecessary weight [Currey, 2002].
2.1.4 Composition

From an engineering materials point of view, bone is classified as a composite. It is composed of both an organic and inorganic phase. Each phase provides a specific property which benefits the overall structure. The organic component confers toughness while the inorganic component ensures stiffness. The organic phase is mostly collagen, existing primarily as type I collagen, with three tropocollagen strands arranged in a triple helical arrangement [Currey, 2002]. Smaller amounts of other types of collagen can also be found, although these are more likely to come from the basement membranes used to attach included cells or from the adventitia that surrounds blood vessels. Some non collagenous proteins also exist, but their function is less well understood. These include proteoglycans and glycoproteins. Of note are osteocalcin and osteonectin, which are produced by osteoblasts. Both are believed to play a role in mineralisation, while osteocalcin also controls calcium ion homeostasis and osteonectin is associated with collagen binding [Kelm et al., 1994]. Osteoblast activity is often measured by the determination of osteocalcin levels [Delmas, 1995]. Other proteins of interest include osteopontin [Denhardt and Guo, 1993], a linking protein, and bone morphogenic proteins [Hodsman et al., 2000], which instigate bone formation.

The inorganic material exists mainly as rods or plates of hydroxyapatite (Ca$_{10}$(PO$_4$)$_6$(OH)$_2$) packed between the collagen helices. The hydroxyapatite is non-stoichiometric and impure.
2.1.5 Bone Remodelling

In order to ensure that the skeleton can continue performing its intended support and protective functions, and maintain the optimal concentrations of stored ions, constant maintenance is required. This maintenance is carried out by two types of cells, osteoclasts and osteoblasts. Osteoclasts act by removing bone. This resorbed bone is then replaced with new bone laid down by osteoblasts (Figure 2.3). An osteoclast working with an osteoblast is referred to a Bone (Re)Modelling Unit (B(R or M)U). In healthy adults, both types of cells seem to work at the same rate. However, during growth deposition exceeds resorption, while beyond maturity resorption exceeds deposition.

![Figure 2.3: The cycle of bone remodelling. The process begins with osteoclasts forming a cutting cone within the space of a couple of days (a). This erosion channel increases in diameter up to approximately 200 µm (b), which takes two weeks. This then progresses along the bone. When the resorption cavity is fully formed, osteoblasts begin to lay down new bone in the form of lamellae (c). This process continues for around three months (d), although mineralisation carries on much longer.](image-url)
2.1.6 Bone Mineral Content

For females, the population of interest in this body of work, bone mineral content follows a characteristic curve with five distinct stages (Figure 2.4). The first two steps represent increases, firstly being a slow increase up to puberty, followed by a faster rate from puberty to maturity. The increase at puberty is due to the increased estrogen levels and growth hormones. The change in mineral content is correlated with the Tanner stage (physical development), even when adjusted for age [Boot et al., 1997]. By late adolescence, bone mineral content is approximately 90% of the peak value [Henry et al., 2004]. A relatively stable period then continues to the age of menopause, with the possibility of consolidation of the bone (an increase in mineral content with no associated change in bone size). It has been demonstrated for a European sample that BMD does not change significantly between the ages of 20 and 49 [Lofman et al., 1997]. Finally, there is a rapid decrease in BMD in the first five to ten years immediately after menopause, due to the oestrogen deficiency, which then continues but at a lower rate [Geusens et al., 1986].

2.2 Osteoporosis

As was stated in Chapter 1, although it is accepted that as we age bones become thinner and less dense, leaving us at a greater risk of a fragility fracture, it is difficult to define the exact stage of osteoporosis in an individual. In early experimentation, biopsy was used to collect samples which could be studied and measured. While this approach may enable a very detailed investigation of the morphology of a bone sample, it is hardly practical as a means for screening the entire population. It is also unethical to expect any number of
Figure 2.4: Bone Mineral Content (BMC) plotted against Age for females. The five typical stages are divided by life events (horizontal light gray lines). The increase of BMC begins slowly up to puberty, followed a faster rate up to maturity. BMC then remains relatively stable until menopause. Immediately after menopause there is a sharp decrease in BMC which usually last between five and ten years. Finally, BMC continues to decline, but at a much lower rate.

healthy people to undergo such an invasive procedure. With the development of radiogrammetry and absorptiometry, which will be explained later, clinicians and researchers were able to measure a variety of parameters known to be affected by osteoporosis. While none of these are perfect, in so far as they only measure one manifestation of osteoporosis, they have been accepted due to the lack of a better system.

The consensus from WHO is that absorptiometry of axial skeleton, by the use of DPA or DXA, is the most significant predictor of fracture risk, and therefore the most appropriate means of predicting osteoporosis [Alexeeva et al., 1994]. Osteoporosis is defined based on BMD measurements (Table 2.1).
2.2.1 Definition

T-score

T-scores are calculated by comparing an individual’s measured BMD with values for a young, healthy reference population (Equation 2.1).

\[
T - \text{score} = \frac{\text{BMD}_{\text{Measured}} - \text{BMD}_{\text{Young Healthy}}}{\text{Standard Deviation}_{\text{Young Healthy}}} \tag{2.1}
\]

Z-score

Another popular means of presenting densitometry results is using Z-scores. Z-scores, unlike T-scores, compare an individual to an age matched population (Equation 2.2).

\[
Z - \text{score} = \frac{\text{BMD}_{\text{Measured}} - \text{BMD}_{\text{Age Matched}}}{\text{Standard Deviation}_{\text{Age Matched}}} \tag{2.2}
\]
2.2. Osteoporosis

reduced. Therefore, that raises the question if we should compare people with those who
are already compromised? The author feels that this is not the best means of determining
risk of fracture or osteoporosis, and as a result analysis will be compared with T-score.

2.2.2 Manifestations

Cortical Bone

As osteoporosis progresses, the cortices of all bones begin to thin. This can continue to
the stage where there is a noticeable, visible decrease [Grampp et al., 1997]. It is gener-
ally accepted this thinning results from the trabecularisation of the inner surface of the
bone. This trabecularisation causes an increase in porosity and a reduction in the overall
strength. For men at least, it has been shown that deposition of bone on the periosteal
surface counteracts this thinning [Duan et al., 2001].

Cancellous Bone

For cancellous bone, mass is reduced by the process of the resorption of trabeculae. Whilst
it was originally thought that thinning of the trabeculae continued until ultimately the
entire strut is resorbed, some research has proposed that this may not be true. Parfitt et al.
[1983] measured the number and thickness of the trabeculae of the iliac crest. They found
that while the number of trabeculae certainly decreased, the thickness of the remaining
trabeculae did not decrease toward zero. It was proposed that thinning is rather more
localised, at the centre of the trabeculae, and causes the ends of the structure to become
separated. Then, the remaining bone is resorbed in a linear fashion along the original long
axis toward the nodes from which it originated. In any case, bone is lost from trabeculae
which do not lie along the main direction of loading of the bone first. This loss of bone, with no loss in overall volume, is what results in the observed decrease in BMD. This is now more broadly accepted [Seeman, 2008].

### 2.2.3 Changes in Mechanical Competency

These changes in bone mass and architecture are only important when we consider the effect of density on the mechanical properties of bone, and in particular cancellous bone. It has been demonstrated that the elastic modulus and ultimate strength of cancellous bone depends on the apparent density [Keaveny, 1993]. The elastic modulus follows a power-law relationship, as per Equation 2.3 [Carter and Hayes, 1977]. In this equation, \( a \), \( b \) and \( c \) are constants that depend on the structure of the bone and \( \rho \) is the hydrated apparent density.

\[
E = a + b\rho^c
\]  

(2.3)

Keaveny [1993] have shown that the \( c \) coefficient is in the order of 2. Figure 2.5 shows the relationship between density and both modulus of elasticity and ultimate strength. The major morbidity associated with osteoporosis is fracture at the hip, lumbar spine and wrist. These sites are primarily cancellous bone whose mechanical properties may be altered by the changes, such as the reduction in bone mass that accompanies the progression of osteoporosis. Simplifying the formula to a more accessible example, a reduction of one quarter of the bone density will represent a 50\% decrease in the ultimate strength. Over a relatively short time, say the first five years post menopause, an individual may go from having normal bones to much more fragile bones. It also reaffirms the need to screen the
population as early as possible, in order to select those at greatest risk and prevent further bone loss.

Figure 2.5: Work carried out by Keaveny [1993] and Zioupos et al. [2008] exemplifies the relationship between the density and both the elastic modulus and the ultimate strength. For both relationships the exponent was approximately two in the principle axis. Figure reproduced with permission form Zioupos et al. [2008].

2.3 Detection of Osteoporosis

There are a very limited number of clinically accepted methods for diagnosing osteoporosis. This is in part due to relatively recent definition for the condition [Alexeeva et al., 1994]. The following section lists the methods that have been used in the past and those used currently. The simplest guidelines for selecting those who require scanning are also introduced.
2.3. Detection of Osteoporosis

2.3.1 Guidelines for DXA screening

A number of large organisations, such as WHO and NOF, have guidelines for selecting those who require DXA scanning. For example, the NOF suggest that anyone over the age 65, anyone over the age of 55 with another risk factor or any postmenopausal woman presenting with a fracture be sent for DXA scanning. Although these guidelines are simple and easy to apply, they can lead to large numbers of women being sent for investigatory scans when they are not required. Possibly the greatest benefit of a quantitative ultrasound screening based approach is the possibility to reduce the number of unnecessary scans. If more, uncross-correlated, information can be determined about an individual, clinicians could reduce the demand on the already overburdened scanning clinics by reducing the number of perfectly healthy people sent for scans.

2.3.2 Radiogrammetry

As was mentioned in the previous chapter, radiogrammetry was the first widely used means of monitoring change in bone mass. It was introduced by Barnett and Nordin [1960] who measured the cortical thickness of the metacarpal. Hand radiographs were taken and measurements were performed at the midshaft of the metacarpal using calipers. One of the following calculations can then be carried out. The metacarpal length can be divided by the width, to give the metacarpal index (MCI). Or the outer (bone) and inner (medullary) diameter are measured, as per Figure 2.6. These are used to calculate the width of the combined cortical bone thickness (CCT), which is bone diameter minus medullary diameter. This does indeed fill the role as a means of monitoring skeletal changes, as it can be used to quantify cortical thinning. However, there are a number
2.3. Detection of Osteoporosis

of disadvantages associated with the use of radiogrammetry. The most notable of these is the fact the investigated site is primarily cortical bone, initially of the metacarpal and then more recently of the radius. This means that the more metabolically active cancellous bone is not investigated, nor are the sites of clinical interest in terms of fracture risk. Even in the cortical bone that is studied, intracortical porosity and trabecularisation of the endocortical surface is not monitored. Possibly the greatest drawback to radiogrammetry, however, is actually not any of these limitations, rather the precision of the measurements. When MCI was first introduced, the coefficient of variation of MCI was 7.4% [Barnett and Nordin, 1960]. Precision values did begin to fall as technology improved and techniques became more computerised. However, even with digitised systems, the values for CCT remained greater than 5% [Kalla et al., 1989]. The problem with poor precision for this technique is that only large changes, at least as large as the coefficient of variation, can be confidently confirmed. This makes monitoring small changes impossible.

More recently there has been development of new measurements based on radiogrammetry. Rosholm et al. [2001] used the bone width and thickness of the radius and metacarpals derived from computerised radiogrammetric techniques to calculate the volume of the projected area, which was in turn used to calculate the estimate mineral density, BMD\textsubscript{DXR}. This value was found to be significantly correlated to the BMD at the hip and spine, and of the same magnitude as the correlations between the BMD from DXA at the site and the BMD at the hip and spine. Furthermore, the coefficient of variations for these estimated density values were 0.6% which makes this method more suited for monitoring small changes.
2.3. Detection of Osteoporosis

2.3.3 SPA and DPA

Cameron and Sorenson [1963] introduced the use of single photon absorptiometry (SPA) as a means of measuring bone mineral content. A beam of $\gamma$-rays are passed through the region of interest and collected by a scintillator. The bone mineral determines the number of photons that are transmitted. The differences in attenuation across the bone and soft tissue and soft tissue alone are equivalent to the mineral content of the bone if the soft tissue is of constant thickness. As this is not the case, the site of interest is scanned in a water bath, where water is assumed to be a soft tissue equivalent. The results are divided by the axial length to give units of g.cm$^{-1}$ which is Bone Mineral Content (BMC). This may also be divided by the area of the scanned region to give the areal Bone Mineral Density (BMD).
2.3. Detection of Osteoporosis

In order to enable the scanning of deeper sites, such as the lumbar spine, Krølner and Nielsen [1980] proposed the use of a source that emits photons at two separate energy levels. Collecting the photons at these two distinct energies level allows for the use of the dual-photon transmission equation, which corrects for the soft tissue. This meant that no tissue equivalent, i.e. water bath, was required and scanning could be performed on the axial skeleton. Absorptiometry at the hip and spine has the obvious advantage of being a direct measurement of sites frequently affected by osteoporosis.

2.3.4 SXA and DXA

More recent advances in the field of absorptiometry has seen a replacement of radionuclide sources with X-ray tubes, leading to the development of Single Energy X-ray Absorptiometry (SXA) and Dual Energy X-ray Absorptiometry (DXA). This is to eliminate the problems of long term precision associated with source decay. SXA has been shown to have low coefficient of variation for measurements at the radius [Berenson et al., 2001], suggesting that it may be useful as a method of measuring skeletal condition. However, as was the case with SPA, SXA requires a water bath as a means of correcting for soft tissue. This makes it cumbersome to use and may add unnecessary time to the duration of scan. DXA works on the same principle as DPA, except it uses x-rays instead of $\gamma$-rays. The use of X-rays allows for faster, more precise measurements [Borders et al., 1988]. A sample DXA printout showing the typical scan and results can be seen in Figure 2.7.
Figure 2.7: Printout of results from Dual Energy X-Ray Absorptiometry scan. The BMC and BMD are given at a variety of sites. The T-scores and Z-Scores are also provided. The graph also plots the individual’s total hip BMD and the expected changes with aging.
2.3.5 Screening Tools

Given the associated costs involved with these techniques, there is a need to make more efficient use of such services. Many different research groups have developed simple, questionnaire based tools for determining the risk of developing osteoporosis.

QUS

SOS Speed of Sound (SOS) measurements were one of the first methods of characterisation proposed employing the passage of ultrasound through bone. Over the years, a number of slightly different means of calculating these speeds have been developed. The basic principles can be seen in Figure 2.8. These begin from the simplest approximation of the Limb Velocity, calculated by dividing the distance between transducers placed either side of the bone in question by the time taken for the emitted wave to be detected by the receiver (Equation 2.4). To attempt to measure only the velocity through the bone the Bone Velocity has also been suggested. This measurement depends on the thickness and time required to cross the soft tissue (Equation 2.5). An extension of these has been developed for use when the limb is placed in a water bath. The velocity of sound through water and the exact separation of the transducers is required (Equation 2.6). Finally, the axial velocity is used to measure the velocity along long, flat areas of bone which are not excessively covered with soft tissue. This velocity is calculated by measuring the time required for the sound wave to propagate along the bone and to be detected by the receiver. The distance between the transmitter and receiver is fixed. Each method has shown some use as a predictor of low bone mineral density and relatively low coefficients of variation. An example of the performance and precision of devices that interrogate the finger can be
Table 2.2: Performance of Speed of Sound Measurements at the Proximal Phalanx

<table>
<thead>
<tr>
<th>Study</th>
<th>Device</th>
<th>Correlation with BMD</th>
<th>Precision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Louis et al. [1998]</td>
<td>DBM Sonic 1200</td>
<td>R = 0.45–0.62</td>
<td>&lt; 2.7%</td>
</tr>
<tr>
<td>Guglielmi et al. [1999]</td>
<td>DBM Sonic 1200</td>
<td>R = 0.56–0.74</td>
<td>&lt; 2.3%</td>
</tr>
<tr>
<td>Scavalli et al. [1997]</td>
<td>DBM Sonic 1200</td>
<td>R = 0.45</td>
<td>0.88%</td>
</tr>
<tr>
<td>Blanckaert et al. [1999]</td>
<td>DBM Sonic 1200</td>
<td>R = 0.03–0.45</td>
<td>0.91%</td>
</tr>
</tbody>
</table>

seen in Table 2.2.

\[
\text{Limb Velocity} = \frac{x}{t_x} \quad (2.4)
\]

\[
\text{Bone Velocity} = \frac{X_b}{t_b} = \frac{x - (xs_1 + xs_2)}{t - (ts_1 + ts_2)} \quad (2.5)
\]

\[
\text{TOF Velocity} = \frac{V_wx}{x - (\Delta tV_w)} \quad (2.6)
\]

**BUA** Langton et al. [1984] published the theory of using Broadband Ultrasound Attenuation (BUA) as way of determining bone condition. A reference curve is produced by collecting a wave that crosses water and plotting its fast Fourier transform. Then, waves from scans of individuals are collected and compared to this reference curve. The difference of these curves are plotted and used to calculated the attenuation with frequency (Figure 2.9). It was noted that greater attenuation was recorded in higher quality bone.
2.3. Detection of Osteoporosis

(a) Contact Method

(b) Substitution Method

(c) Along The Bone

Figure 2.8: Speed of Sound may be calculated by means of through transmission (a and b) or along the shaft of longer bones (c).
2.3. Detection of Osteoporosis

2.3.6 Questionnaire Based Assessment Tools

A number of attempts have been made to derive very simple tools for diagnosing osteoporosis consisting only of a questionnaire administered by a health care worker. The potential benefits of this type of approach are obvious. The greatest advantage is the cost of the ‘test’. A simple questionnaire could be completed by all postmenopausal women attending their general practitioner at virtually no cost. This could prioritise those potentially at greatest risk, while deferring possible further investigation of those at lowest risk.

The OST, developed by Koh et al. [2001], was one of the first of this kind published. The authors looked at postmenopausal sample of east Asian women recruited from the community. Details of risk factors were self reported and BMD measurements were taken the left femoral neck. With the suggested threshold, they found that the tool performed moderately to well. However the authors suggest that the two separate cut-offs should be
used, categorising those as either high, intermediate or low risk.

The SCORE tool was developed to predict those with low (T-score $\leq -2.0$) at the femoral neck [Lydick et al., 1998]. The sample in question was a Caucasian sample from North America. Race, the presence of rheumatoid arthritis, the use of oestrogen therapy, previous fractures, age and weight were all selected as significant risk factors. A validation study supported the promising results found during development.

The ORAI tool found that age, weight and oestrogen use were the most important factors for a Canadian population [Cadarette et al., 2000]. Results from development and validation sample showed the tool had good predictive ability. The test was designed to discriminate between patients with normal and low (T-score $\leq 2.0$) mineral density. It performed the task quite well, with a specificity of approximately 50%. This means that 50% of all healthy individuals who are incorrectly sent for DXA scans could be asked to return at a later date, thereby making more efficient use the services.

The tool developed for a population closest to the British population is possibly the OSIRIS. Sedrine et al. [2002] found that for postmenopausal, Belgian women between the ages of 60 and 80 years old, weight, previous fracture and oestrogen use were best at selecting those with osteoporosis. The first implementation showed the tool had some use, with good accuracy. However, the authors believe that it is best not to determine healthy or osteoporotic, rather high, medium or low risk. Those with values in the low risk range being reassessed later and those at high risk being immediately been prescribed treatment. It was suggested that those at medium risk would be further investigated to determine if treatment was necessary at that point.
2.3.7 Questionnaire Based Tools for Predicting Fracture

Similar methods have been employed to predict fracture. In a study by Black et al. [2001] the authors looked at questionnaire results along with measured variables to determine which were the most significant for predicting fracture at a number of sites. They found that age, history of fracture, history of maternal fracture, weight, smoking status and the need for help when getting out of a chair proved to be the most significant and least inter-correlated. In cases where BMD measurements are available, they also are added to the model. The simple assessment performed moderately well, but significantly better when BMD was included.

The newest tools to be developed for determining the probability of fracture is FRAX [Kanis et al., 2008]. Age, sex, BMI, history of fracture, family history of fracture, glucocorticoid use, presence of rheumatoid arthritis, secondary osteoporosis and smoking and alcohol consumption were compared to osteoporotic fracture of any type. These were then used to calculate the probability of hip fracture and fracture of any type. This may not give an indication of the BMD, but long term studies might prove that making decisions based on the probability of fracture are more appropriate than on density alone.

2.4 Statistics

The previous section describes the major techniques, past and present, which have been used to determine changes associated with bone loss. Although these approaches measure different parameters at a variety of skeletal sites, it is imperative to evaluate how precise a technique is in order to be able to have confidence in the results it provides. There
is also a need to be able to compare how well different methodologies correctly diagnose osteoporosis. This is to determine if, for example, new ideas or devices perform better than existing ones. The following section describes the statistical techniques used currently in the field of densitometry and the means of comparing tools that assess risk of osteoporosis and risk of fracture.

2.4.1 Precision

Precision is a numeric expression of the reproducibility of a measurement. It can be imagined as the variation and spread of the values when a set of measurements is taken by the same, or different, observer for the same input with repositioning between measurements. This is not to be confused with repeatability which looks at the spread of data when there is no repositioning between measurements. Although repeatability is important, as it can tell if a machine is likely to produce reasonable results, the major sources of errors are expected to be due the inconsistent selection of the exact region of interest by one observer and the differing opinion of the exact region of interest between different observers.

Precision for an Individual

The easiest means of calculating precision for a densitometric technique is to perform a number of repeated scans on the same individual whilst repositioning the site of interest before each scan. This allows for the calculation of precision error of that specific method of measurement for that specific individual. This is simply the standard deviation of \( i \) repeated measurements of individual \( j \) (See Equation 2.7).
2.4. Statistics

\[ SD_j = \sqrt{\frac{\sum_{i=1}^{n_j} (x_{ij} - \bar{x}_j)^2}{n_j - 1}} \] \hspace{1cm} (2.7)

From this equation, \( x_{ij} \) refers to the \( i^{th} \) measurement for individual \( j \). Also, \( \bar{x}_j \) represents the mean of all measurements for individual \( j \) and \( n_j \) corresponds to the number of repeated measurements.

In order to make precision errors more intuitive, they may be expressed as a coefficient of variation (See Equation 2.8). This also has the advantage of incorporating the mean measured value, which takes into account the scale of the precision error. To illustrate this point, imagine one were investigating the speed of sound at the heel and the radius as a means of predicting density. Imagine if the mean values were 1600 m.s\(^{-1}\) and 2000 m.s\(^{-1}\) respectively and the standard deviation were both 20 m.s\(^{-1}\). Although the techniques have an identical precision error, the coefficient of variation is greater for the heel (1.25%), than for the radius (1%). This simply reflects that fact that the standard deviation represents a greater proportion of the mean heel value.

\[ CV_{SD_j} = \frac{SD_j}{\bar{x}_j} \times 100\% \] \hspace{1cm} (2.8)

However measuring only one individual limits what can be said about the precision of the technique in general. It may be the case that the individual that was scanned had an exceptionally symmetric, homogenous region of interest. Therefore the calculated precision values may be overly optimistic, or pessimistic, compared the true value for the entire population. Alternatively, the scanned subject may have suffered a fracture or other deformity at the scan site without their knowledge, which could lead to extremely varied,
imprecise results. Therefore, the precision of a technique is generally calculated by looking at results from more than one subject.

Precision of a Technique

The precision error of the technique is the root-mean-square average of the precision errors of each individual, as per Equation 2.9, where \( m \) is the number of subjects scanned. It is important to note that the precision error of the technique is not the mean of all the subjects’ precision errors, rather the squared precision error is given by the mean of their variances [Glüer et al., 1995].

\[
SD = \sqrt{\frac{\sum_{j=1}^{m} SD_j^2}{m}}
\]  

(2.9)

The coefficient of variation for a technique is calculated using the standard deviation found for the technique. The averages for each individual, \( \bar{x}_j \), and the number of individuals, \( m \), are required for this computation (See Equation 2.10).

\[
CV_{SD} = \frac{SD}{\sum_{j=1}^{m} \frac{\bar{x}_j}{m}} \times 100\%
\]  

(2.10)

The above calculation of SD assumes that the same number of repeat measurements are performed on all the subjects. In practice, this may not be the case and Equation 2.11 represents the general expression of the formula.

\[
SD = \sqrt{\sum_{j=1}^{m} \sum_{i=1}^{n_j} \frac{(x_{ij} - \bar{x}_j)^2}{df}}
\]  

(2.11)

The degrees of freedom, \( df \) from above, for the technique is the sum of the degrees of freedom.
freedom of the scans for the individuals, as per Equation 2.12.

\[
df = \sum_{j=1}^{m} (n_j - 1)
\]  

(2.12)

There are two important influences that need to be addressed when presenting the precision of a technique. The first of these has been alluded to previously; the effect of the sample on the precision error. More specifically, how the health of the sample effects the calculation of precision. There is a general agreement, at least within densitometric circles, that the precision error will be smaller for healthy subjects compared to osteoporotic individuals. Therefore when precision errors are quoted, it is important to also state the health of the sample. The second influence that needs to be dealt with is the time frame of the measurements. The above procedure is only appropriate for calculating the short term precision of a technique. Generally, these repeated measurements are performed within three to four weeks. It is obvious that if the window for scanning was years instead of days or weeks, there may in fact be a significant reduction in the parameter that was to be measured, which would increase the recorded precision error.

Detectable Differences

While the precision errors and the coefficients of variation provide very important information about the measurements of a methodology, they are also used to calculate what change can be deemed significant and the length of time before a change might be noticeable. An excellent review has been written by Glüer [1999], the main points of which are presented here.
**Least Significant Change**  As the name suggests, the Least Significant Change (LSC) is the smallest difference that can be attributed to actual changes in the skeletal quality. Of course, the degree of confidence that is most applicable needs to be decided to determine this value. Assuming the certainty must be greater than 95%, then the minimum difference that can be detected must be 2.8 times the value of the precision error (Equation 2.13).

\[
LSC = 2.8 \times PE
\]  

\[(2.13)\]

**Trend Assessment Margin**  In a research setting, the use of the LSC can be used, for example, to detect changes in BMD due to new drug treatments. In the clinical world however, it may not be suitable to wait until this change has taken place. A clinician may concede that detrimental changes are occurring at a lower confidence level, if it is required to prescribe treatment as soon as possible. This has led to the development of the Trend Assessment Margin (TAM) (Equation 2.14). Trend implies that the certainty is less than for a significant change. Indeed, a certainty of 80% is usually accepted.

\[
TAM = 1.8 \times PE
\]  

\[(2.14)\]

**Followup Intervals**  The LSC and TAM are also used to answer the question of what period of time should there be between scans. It is intuitive that which input is used will affect the time. Which is used depends on whether it is important to guarantee that a change is occurring, or whether there is a trend developing. The Monitoring Time Interval (MTI) is the time point when it is expected that half of the population will display a change greater than the least significant change (Equation 2.15).
\[ MTI = \frac{LSC}{\text{Median Change per Annum}} \] (2.15)

The Trend Assessment Interval (TAI) is the time point when half the population will display a change greater than the trend assessment margin (Equation 2.16). This will be shorter than the monitoring time interval, but there is slightly less certainty that the difference is real.

\[ TAI = \frac{TAM}{\text{Median Change per Annum}} \] (2.16)

### 2.4.2 Evaluation of New Diagnostic Tools

One of the goals of this work is to produce assessment tools which evaluate an individual’s risk factors and classifies them as either healthy or osteoporotic. However, simply creating these tools is not enough: each must be assessed to determine if it is more, or less, effective than similar tools. Typically, the results of new or proposed diagnostic tools or interventions are compared for a sample of patients with and without the diseased state. This is simple where one can easily distinguish between these states. For example, if a drug that attempts to reduce blood pressure were being evaluated, simply measuring blood pressure would indicate to the researcher if the drug had been successful or not.

This is not the case for judging the success of diagnostic tools for osteoporosis. The problem lies in the fact that osteoporosis is not perfectly defined. Although it is accepted as a state of low bone mineral content that increases the risk of fragility fracture, there are still no unequivocal guidelines when it comes to classifying somebody as osteoporotic. As was discussed previously, absorptiometric T-scores are used in lieu of any better methodology.
Therefore, DXA measurements are used to confirm or deny the presence of the disease. This type of test is referred to as a gold standard, and is common in medicine where certain procedures are regarded as definitive.

Assuming then that DXA is the gold standard, the effectiveness of a new test, let us call it Test A, is assessed using binary classification. Figure 2.10 shows a sample scenario where Test A is evaluated. When both DXA and Test A identify an individual as positive for osteoporosis, they are a True Positive (TP). Similarly, a True Negative (TN) comes about when both tests indicate the absence of osteoporosis. There is also the possibility of two distinct types of error; a type I error and a type II error. A type I error, also known as a False Positive (FP), occurs when Test A suggests the presence of osteoporosis in a healthy individual. A type II error, or False Negative (FN), arises when a diseased individual is given a clean bill of health by Test A.

This type of plot allows the researcher to visualise how well the data are correlated, but also helps in determining the appropriate threshold to set for the new test. Setting this threshold is dependent on the possible outcomes of the above mentioned errors. Imagine a simplified case where there are healthy and diseased individuals. There is also a cure for this disease and a new diagnostic tool which may be used to test for it. Now imagine two possible scenarios. The first assumes that the symptoms of the disease are easily managed and although the cure is effective, it has some adverse side effects. It is then extremely important not to prescribe treatment to healthy individuals, type I errors. This is achieved by setting the threshold for the new test such that all healthy individuals are selected as such (in Figure 2.10, moving the vertical threshold to the left). In the second scenario imagine that if the cure is not prescribed to a diseased individual they will suffer greatly
and that the cure has no side effects. Here the emphasis is on ensuring that no diseased individuals are misdiagnosed as healthy, type II errors. This is accomplished by applying a threshold that ensures diseased individuals are recognised as such (in Figure 2.10, moving the vertical threshold to the right).

It is obvious that no test (expect one that is 100% accurate) can have a threshold that will satisfy both of these conditions. Researchers must therefore judge which type of error poses the greater problem and minimise this, at the expense of more of the other type of error. It is not simply good enough to accept that some error will be present. There must be some measurement of the proportion of False Negatives and False Positives. This is done by constructing a confusion matrix like that in Table 2.3.
2.4. Statistics

Table 2.3: A Confusion Matrix. This type of matrix is used to display the differences between the test values (Test A) and the true or gold standard values (DXA in this case).

<table>
<thead>
<tr>
<th>Test A</th>
<th></th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>False Positive (FP)</td>
<td>TN + FP</td>
</tr>
<tr>
<td></td>
<td>True Negative (TN)</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>True Positive (TP)</td>
<td>TP + FN</td>
</tr>
<tr>
<td></td>
<td>False Negative (FN)</td>
<td></td>
</tr>
</tbody>
</table>

With this data, the sensitivity and specificity are calculated. The sensitivity is a measure of how well a test diagnoses diseased individuals correctly (Equation 2.17). Conversely, the specificity of a test determines the ability of any test to select the healthy individuals (Equation 2.17).

\[
\text{Sensitivity} = \frac{TP}{TP + FN}, \quad \text{Specificity} = \frac{TN}{FP + TN} \tag{2.17}
\]

In a clinical setting, there is also a desire to know the probability of a person having, or not having, a disease based on a positive, or negative, results from a given test. The Positive Predictive Value (PPV) and the Negative Predictive Value (NPV) are used to calculate these probabilities (Equation 2.18).

\[
\text{PPV} = \frac{TP}{TP + FP}, \quad \text{NPV} = \frac{TN}{FN + TN} \tag{2.18}
\]

The above techniques were developed to analyse the errors associated with new diagnostic tests. They do not, however, measure the effectiveness of the test. To do this, this information must be manipulated further. Receiver Operating Characteristic (ROC) curves, plots of sensitivity versus 1 - specificity, are used to monitor the effect of moving
the decision threshold (dashed, vertical line from Figure 2.10) of the test. This is done by assuming that the decision threshold is to the left of all points, where sensitivity is 0 and specificity is 1. Then by incrementally moving the threshold to the right, until sensitivity is 1 and specificity is 0, as per Figure 2.11.

![Figure 2.11: The solid curve represents the diseased population and the dotted curve represents the healthy population. The decision threshold, the dashed line, is moved to the right, whilst calculating the sensitivity and specificity at each step. These values are then used to plot the ROC Curve.](image)

Plotting the sensitivity versus 1 - specificity gives a ROC curve, something like Figure 2.12. For a test that performs very well, i.e. has very few errors of either type, the curve will begin at (0,0), approach (0,1) and terminate at (1,1). This is because, if there are few false positives or false negatives, sensitivity and specificity can both be high for most decision thresholds. The Area Under the Curve (AUC) is calculated by integrating the ROC curve. The test in Figure 2.12 has an AUC of 0.84. Similarly, a test that randomly diagnoses people as normal or healthy, such as the dashed line in Figure 2.12, will have an AUC of 0.5. Tools or tests with an AUC of 0.5–0.6 are considered to have little or no discriminatory ability.
Figure 2.12: A sample ROC curve. The solid line represents the curve for a imaginary test. The dashed line form (0,0) to (1,1) would be the performance of a test that randomly assigns the result; for example if diagnosis was made based on a coin toss. A perfect test would include the point (0,1), as this suggests that for a single decision threshold sensitivity and specificity are both 1, with no false positives or false negatives.

Values of 0.6–0.7 are deemed poor, 0.7–0.8 moderate and 0.8–0.9 good. Any diagnostic tool with an AUC value between 0.9 and 1 is considered excellent.
Questionnaire Based Analysis

Make everything as simple as possible, but not simpler

Albert Einstein

One can tell quite a number of things by simply using a detective method and by focussing on details and ‘tell tale’ signs of osteoporosis. By leading a person through a set of questions, a GP can paint a picture of their overall risk. However, this may not be reassuring enough for those who rely on expensive machinery to diagnose conditions. The idea of just collecting patient responses may seem outdated when it is possible to measure the attenuation of x-rays through their bones. Therefore, these ‘technophiles’ may be disappointed and surprised to find out that such response based assessment tools have a proven track record for distinguishing those with a higher probability of fragility fracture. To add insult to injury, these most basic of assessments have also been shown to select those with osteoporosis, based on absorptiometric techniques, quite well. This chapter details an attempt to do just this for a cohort from within the British population. It also describes how combinations of these risk factors and quantitative ultrasound may be employed to improve the utility, over what can be achieved when either method is
employed individually. Ultimately, the goal is to develop a future questionnaire which will yield a numerical output, which is summative, that can be used to aid with decisions regarding treatment or further diagnostic testing.

### 3.1 Introduction

The key to treating osteoporosis is to determine an individual’s risk as early as possible. Ideally, all women would be assessed close to, or soon after, menopause in order to measure their bone mineral density before the initial rapid decrease in bone mineral content. This would allow clinicians to document a density starting point before the expected rapid decrease, and determine if an individual began at a compromised level. Also, follow up assessments at regular intervals would allow a physician to gauge the rate of bone loss and to judge whether the individual had become, or was in danger of becoming, osteoporotic.

Although are there a number of means of diagnosing osteoporosis (Chapter 2), DXA scanning of the spine and hip remains the gold standard. This method of densitometry is widely used in assessing bone mineral density for many ethnic groups of all ages. There are however a number of disadvantages which may limit the availability or appropriateness of this technique. The most obvious of these is the associated costs. These machines are very expensive to purchase, maintain and operate, meaning that they are not readily available in all regions. In the UK alone there is a deficit of such scanners, and in extreme cases individuals may have to wait for up to 78 weeks to be seen [APPOG, 2005]. There is also the issue of exposing people to sources of ionising radiation. Even if the doses are relatively low [Njeh et al., 1999a], it may not be justified to perform repeat scans on
healthy individuals. With these shortcomings in mind, there have been efforts to minimise the numbers sent for DXA scanning. These efforts are very varied in approach.

Many groups and organisations suggest that all women who present with, or exceed, a certain risk criteria should be sent for DXA scanning. These criteria may be quite simple, for example all women over the age of 65 as prescribed by the National Osteoporosis Foundation. However, even less specific tools have also been offered. Weinstein and Ullery [2000] suggested that women over the age of 65, OR with a weight of 140 lb or less at the time of menopause OR those you have never used oestrogen be referred for investigation. These rather crude techniques, coupled with an aging population would mean that these tools have little use at decreasing the numbers sent for DXA scanning. In fact, every woman would be selected eventually, whether they had osteoporosis or not. Therefore, due to the overall inefficiency, this basic approach is not favoured.

The next advance, following this methodology, was to combine the different risk factors in order to derive a scoring system that would allow for the categorising of people by their perceived risk of osteoporosis. This type of system meant that fewer healthy people would be sent for scanning. For example, one of the simplest tools based on more than one risk factor was the OST (Osteoporosis Self-assessment Tool), developed by Koh et al. [2001]. The authors looked a combination of weight and height of Asian women and compared these to the BMD T-Score at the hip. The obvious advantage of this combinatory approach is that it looks at more than one risk factor. This means that, for example, even if a woman is over a certain threshold age, she may be protected from osteoporosis by her body weight or vice versa. Implementing this test would reduce the number of unnecessary scans significantly. However, the tool must be designed specifically for the population
3.1. Introduction

in question. Examples such as SCORE (Simple Calculated Osteoporosis Risk Estimation) [Lydick et al., 1998] and OSIRIS (OSteoporosis Index of RISk) [Sedrine et al., 2002] exist for North American and Belgian women.

For many years now, the use of ultrasound as a pre-screening tool for osteoporosis or fracture has been studied in clinical environments. The speed of sound (SOS) through bone was believed to alter with the density and elasticity, and thus could be used to select those with low bone mineral density. Ever since Langton et al. [1984] first introduced the use of broadband ultrasound attenuation (BUA) as a means of quantifying bone health, it has been shown to have a very good concordance with BMD at the hip and spine [Kung et al., 2003, Hadji et al., 1999, Damilakis et al., 2004]. The attenuation depends on the density and connectivity of the cancellous bone of the heel and alters with the resorption of trabeculae [Hans et al., 1995]. Due to the fact that the heel is mainly composed of the metabolically active cancellous bone and is weight bearing it is expected that there would such a good agreement with DXA measures [Greenspan et al., 1997]. Indeed, the ability of velocity and attenuation measurements, from two commercially available scanners, to predict BMD has been recently been studied for a British population [Cook et al., 2005]. The authors found significant relationships between all QUS measurements and BMD T-scores.

The author felt that the next logical step was to combine a knowledge of risk factors with an ultrasound measurement. This has been investigated to a much lesser extent. Richy et al. [2004], for example, developed the ORACLE tool which combined UBPI at the proximal phalanx with certain known risk factors. They found better results than could be achieved with either technique alone. It was thought that while this may have saved a number of unnecessary scans, even greater reductions could be noted if better performing
3.2 Methods

3.2.1 Sample

Volunteers were recruited from those attending the DXA scanning clinic at The Great Western Hospital, Swindon, UK. Ethical approval was granted by the hospital’s ethics board prior to commencement. All volunteers were sent an information sheet prior to arrival at the hospital and provided written informed consent (Appendix C) before they were included in the study. A total of 274 postmenopausal (natural and surgical) Caucasian women were scanned. Volunteers were excluded from the study if they presented with any secondary cause of osteoporosis. This was the case for eight individuals (five with Coeliac disease, two with hyperthyroidism and one with Cushing’s syndrome).

3.2.2 Design and Execution of Questionnaire

Each volunteer was asked to complete a questionnaire (Appendix A). The questionnaire was based upon a previous NHS questionnaire and related to an individual’s physical measurements, lifestyle, diet and medical and reproductive history. A breakdown of the
3.2. Methods

A questionnaire can be seen in Table 3.2.

Based on the responses of the questionnaires, 23 individuals were removed from further study due to a lack of required responses. A further eight individuals were removed from the study due to incomplete or ambiguous medical details. This resulted in a total of 235 volunteers who were considered for analysis. Demographics of the final sample are presented in Table 3.1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (± SD) or Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>59.7 (± 10.8)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.6 (± 12.4)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.0 (± 7.2)</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>25.4 (± 4.6)</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>32 (13.6%)</td>
</tr>
<tr>
<td>Age at Menarche (Years)</td>
<td>13.0 (± 1.9)</td>
</tr>
<tr>
<td>Age at Menopause (Years)</td>
<td>44.8 (± 8.0)</td>
</tr>
<tr>
<td>History of Non Traumatic Fracture†</td>
<td>76 (32.3%)</td>
</tr>
<tr>
<td>Use of Hormone Replacement Therapy‡</td>
<td>109 (46.4%)</td>
</tr>
</tbody>
</table>

† Non Traumatic Fracture was defined as a fracture resulting from minimal trauma based on the questionnaire responses
‡ Hormone Replacement Therapy was assigned if the subject had been using it for ≥ 1 year and treatment began before the age of 60

3.2.3 DXA Scanning

DXA scans for each individual were performed by one of two qualified radiographers. The DXA scanning system was a Hologic QDR-4500C (Hologic Inc., Bedford, Mass.). The system measured BMD values for the lumbar spine, femoral neck and total hip. It then
**Table 3.2: Breakdown of Questionnaire Used**

<table>
<thead>
<tr>
<th>Section</th>
<th>Parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volunteer Details</strong></td>
<td>Weight</td>
</tr>
<tr>
<td></td>
<td>Height</td>
</tr>
<tr>
<td></td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td>Ethnicity</td>
</tr>
<tr>
<td><strong>Physical Activity</strong></td>
<td>Activity at Work and Leisure</td>
</tr>
<tr>
<td></td>
<td>Exercise History</td>
</tr>
<tr>
<td><strong>Lifestyle</strong></td>
<td>Smoker (Past or Present)</td>
</tr>
<tr>
<td></td>
<td>Alcohol Consumption</td>
</tr>
<tr>
<td><strong>Medical History</strong></td>
<td>History of Fracture</td>
</tr>
<tr>
<td></td>
<td>Family History of Osteoporotic Fracture</td>
</tr>
<tr>
<td></td>
<td>Family History of Osteoporosis</td>
</tr>
<tr>
<td></td>
<td>Confinement to Bed</td>
</tr>
<tr>
<td></td>
<td>Medical Problems</td>
</tr>
<tr>
<td></td>
<td>Steroid Use</td>
</tr>
<tr>
<td><strong>Diet</strong></td>
<td>Weight Control</td>
</tr>
<tr>
<td></td>
<td>Calcium Supplements</td>
</tr>
<tr>
<td></td>
<td>Dietary Restrictions</td>
</tr>
<tr>
<td></td>
<td>Variety of Diet</td>
</tr>
<tr>
<td></td>
<td>Dietary Problems</td>
</tr>
<tr>
<td><strong>Reproductive History</strong></td>
<td>Parity</td>
</tr>
<tr>
<td></td>
<td>Breast Feeding</td>
</tr>
<tr>
<td></td>
<td>Menarche</td>
</tr>
<tr>
<td></td>
<td>Menopause</td>
</tr>
<tr>
<td></td>
<td>Hysterectomy</td>
</tr>
<tr>
<td></td>
<td>Oophorectomy</td>
</tr>
<tr>
<td></td>
<td>Oral Contraception</td>
</tr>
<tr>
<td></td>
<td>HRT</td>
</tr>
</tbody>
</table>
used the relevant system database to calculate the T-score for each site. It is these T-scores which were used for analyses throughout this chapter.

3.2.4 QUS Scanning

Two QUS systems were used to measure parameters at a variety of skeletal sites. The CUBA Clinical (McCue PLC, Winchester, UK) was used to measure Velocity of Sound (VOS) and Broadband Ultrasound Attenuation (BUA) across the calcaneus. Speed of Sound measurements were also taken at the proximal phalanx of the third digit (SOS\textsubscript{PP}), the distal radius (SOS\textsubscript{DR}) and the mid-shaft tibia (SOS\textsubscript{MT}) with the Sunlight Omnisense (Sunlight Medical, Rehovot, Israel). Aquasonic\textregistered Clear Ultrasound Gel (Parker Laboratories Inc, Fairfield, N.J.) was used to guarantee coupling between the scanning systems and the investigated sites.

Both devices were quality checked on each day of scanning using quality standards provided with the machines. All QUS scans were taken by the same researcher who was familiar with the operation of both scanning systems.

3.2.5 Statistics

The precision of all QUS measurement techniques was calculated. This entailed calculating the coefficient of variation (CV) for each of the methods, as described by Glüer et al. [1995].

Simple regression analysis was performed between all questionnaire responses and DXA T-scores. This allowed for the determination of the most significant risk factors. Regression analysis was also performed between the QUS variables and the T-scores. Using the most significant risk factors (P < 0.2) for each DXA measurement site as a possible in-
3.2. Methods

dependent variable, and the DXA T-scores as the dependent variables, stepwise (both forward and backward) regression was performed. The stepwise regression involved adding variables to, or subtracting variables from, a model in order to find the best predictors. A significance level of $P < 0.05$ was chosen for addition to or removal from models.

ROC analysis was used to compute the clinical utility of the derived models. In order to create these curves, the sensitivity and specificity values were calculated for varying cutoff thresholds. Also, the cutoff which ensured a sensitivity of $\geq 90\%$ was recorded. The corresponding specificity, PPV and NPV were noted at this level at each DXA site.

3.2.6 Simplification

In order to create tools with some clinical use, certain simplifications were required. The first step was to select the best performing models, based on AUC values, which use questionnaire responses or a combination of questionnaire responses and QUS parameters. The model based on QUS alone was not simplified, as it was assumed if QUS was available then a questionnaire could also be administered.

The simplification process involved scaling and rounding the coefficients of the stepwise regression. This resulted in a more manageable multivariate regression. The AUC values of the simplified models were also calculated to determine if utility had decreased as a result of the simplification. The cutoff which ensured a sensitivity of $\geq 90\%$ was also noted.
3.2.7 Software

All questionnaire data were collected and stored in Microsoft Excel spreadsheets. Regression analysis was performed using MINITAB Statistical Software release 13.31. All other statistical analysis and graphing were carried out using SigmaPlot for Windows 10.0.

3.3 Results

3.3.1 DXA T-scores

Figure 3.1 shows the T-scores of the various DXA sites plotted against one another. The correlations between the lumbar spine and the femoral neck and between the lumbar spine and total hip were similar (\( R = 0.702 \) and \( R = 0.704 \), both at \( P < 0.001 \)). The correlation between the femoral neck and the total hip was higher (\( R = 0.910 \), for \( P < 0.001 \)).

3.3.2 Simple Regression

The results of the simple regression can be seen in Table 3.3. Only variables significant at a level of \( P < 0.2 \) are shown. Even if two variables were derived from similar information (for example frequency and quantity of alcohol consumption), both are presented. Stepwise regression has the ability to determine if the two variables are cross-correlated, and if so, choose the more significant of the two.
3.3. Results

(a) Femoral Neck Plotted Against Lumbar Spine

(b) Total Hip Plotted Against Lumbar Spine

(c) Femoral Neck Plotted Against Total Hip

Figure 3.1: Comparison of DXA T-scores from measured sites.
Table 3.3: Results of simple regression between questionnaire responses and DXA T-scores. Results are given for lumbar spine, femoral neck and total hip

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lumbar Spine</th>
<th>Femoral Neck</th>
<th>Total Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P</td>
<td>R</td>
</tr>
<tr>
<td>Age</td>
<td>-0.333</td>
<td>0.000</td>
<td>-0.453</td>
</tr>
<tr>
<td>BMI</td>
<td>0.210</td>
<td>0.001</td>
<td>0.420</td>
</tr>
<tr>
<td>Height</td>
<td>0.253</td>
<td>0.000</td>
<td>0.202</td>
</tr>
<tr>
<td>Weight</td>
<td>0.333</td>
<td>0.000</td>
<td>0.510</td>
</tr>
<tr>
<td>Physically Active</td>
<td>0.226</td>
<td>0.007</td>
<td>0.197</td>
</tr>
<tr>
<td>Alcohol (Frequency)</td>
<td>0.200</td>
<td>0.023</td>
<td>0.190</td>
</tr>
<tr>
<td>Alcohol (Units per Week)</td>
<td>-0.152</td>
<td>0.019</td>
<td>-0.138</td>
</tr>
<tr>
<td>History of Broken Bones</td>
<td>-0.224</td>
<td>0.001</td>
<td>-0.200</td>
</tr>
<tr>
<td>Broken Bones (Quantity)</td>
<td>-0.155</td>
<td>0.017</td>
<td>-0.182</td>
</tr>
<tr>
<td>History of Non Traumatic Fracture†</td>
<td>-0.327</td>
<td>0.000</td>
<td>-0.281</td>
</tr>
<tr>
<td>Seriously Controlled Weight</td>
<td>-</td>
<td>NS</td>
<td>0.158</td>
</tr>
<tr>
<td>Ca Supplements</td>
<td>-0.205</td>
<td>0.002</td>
<td>-0.148</td>
</tr>
<tr>
<td>Age at Menarche</td>
<td>-0.182</td>
<td>0.005</td>
<td>-0.239</td>
</tr>
<tr>
<td>Age at Menopause</td>
<td>-</td>
<td>NS</td>
<td>-0.170</td>
</tr>
<tr>
<td>Years Since Menopause</td>
<td>0.255</td>
<td>0.000</td>
<td>0.335</td>
</tr>
<tr>
<td>Oophorectomy</td>
<td>0.176</td>
<td>0.007</td>
<td>0.126</td>
</tr>
<tr>
<td>Oral Contraceptive Pill</td>
<td>0.228</td>
<td>0.000</td>
<td>0.245</td>
</tr>
<tr>
<td>Hormone Replacement Therapy‡</td>
<td>0.319</td>
<td>0.000</td>
<td>0.266</td>
</tr>
</tbody>
</table>

† Non Traumatic Fracture was defined as a fracture resulting from minimal trauma based on the questionnaire responses
‡ Hormone Replacement Therapy was assigned if the subject had been using it for ≥ 1 year and treatment began before the age of 60

3.3.3 Precision of QUS Devices

The CV for the Sunlight Omnisense and the CUBA Clinical measurements were all less than 5%. The CV values for $SOS_{PP}$, $SOS_{DR}$ and $SOS_{MT}$ were 1.06%, 0.67% and 0.67%
3.3. Results

Table 3.4: Simple Regression between QUS and DXA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lumbar Spine</th>
<th>Femoral Neck</th>
<th>Total Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R</td>
<td>P</td>
<td>R</td>
</tr>
<tr>
<td>BUA</td>
<td>0.566</td>
<td>0.001</td>
<td>0.616</td>
</tr>
<tr>
<td>VOS</td>
<td>0.505</td>
<td>0.001</td>
<td>0.503</td>
</tr>
<tr>
<td>SOS(_{DR})</td>
<td>0.339</td>
<td>0.001</td>
<td>0.283</td>
</tr>
<tr>
<td>SOS(_{PP})</td>
<td>0.330</td>
<td>0.001</td>
<td>0.374</td>
</tr>
<tr>
<td>SOS(_{MT})</td>
<td>0.221</td>
<td>0.005</td>
<td>-</td>
</tr>
</tbody>
</table>

* NS: Not Significant at P < 0.05

respectively, while the values for VOS and BUA were 0.27% and 3.06%.

3.3.4 QUS

The results of the regression analysis between the QUS devices and the DXA are presented in Table 3.4. The T-score at the lumbar spine was significantly correlated to all QUS measurements. BUA at the calcaneus showed the greatest correlation coefficient with all DXA measurement sites. The SOS\(_{MT}\) showed the weakest correlation with the values for lumbar spine (0.221 at P < 0.005) and showed no significant relationship with BMD from either the femoral neck or total hip.

3.3.5 Stepwise Regression

The stepwise regression provided three models to predict DXA T-score at each site. The first was based on the responses from the questionnaires. The second was created by using the QUS measurements as the independent variables. The final model was derived using
a combination of questionnaire responses and QUS measurements.

All models based solely on the questionnaire responses selected age, weight, a history of non-traumatic fracture and hormone replacement therapy as significant predictors. For the QUS models, BUA was selected as the single predictor of T-score at all sites. The models based on both questionnaire responses and QUS selected similar variables as those for questionnaire responses alone. However, for the lumbar spine BUA was selected and age became insignificant. For both the femoral neck and total hip, VOS replaced hormone replacement therapy. These models can be seen in Table 3.5.

3.3.6 ROC Analysis

The ROC curves were plotted for the equations of Table 3.5. The resultant curves can be seen in Figure 3.2. The AUC (95% Confidence Intervals) values for the models using only the questionnaire responses are 0.79 (0.71–0.87), 0.85 (0.78–0.92) and 0.85 (0.77–0.92) for the lumbar spine, femoral neck and total hip respectively. Using the QUS variables, the values were 0.79 (0.72–0.85), 0.90 (0.84–0.96) and 0.90 (0.84–0.96). The combination models had the highest values; 0.82 (0.75–0.89), 0.92 (0.87–0.96) and 0.93 (0.89–0.97).

3.3.7 Sensitivity and Specificity

The specificity, at a sensitivity of 90% or more, of the best performing models of each type are presented in Table 3.6. The PPV and the NPVs are also presented. It can be seen that the specificities are greatest when both questionnaire responses and QUS are used.
Table 3.5: Results of stepwise regression. The results may be for forward or backward stepwise regression and are chosen based on which accounts for more of variance of the T-score.

<table>
<thead>
<tr>
<th>DXA Site</th>
<th>Model</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Questionnaire Responses</strong></td>
<td></td>
</tr>
<tr>
<td>Lumbar Spine</td>
<td>T-score = - 2.5534 + (0.0372 Weight) - (0.7694 NTF) + (0.6217 HRT) - (0.0218 Age)</td>
<td>31.14%</td>
</tr>
<tr>
<td>Femoral Neck</td>
<td>T-score = - 2.0458 + (0.0374 Weight) - (0.0294 Age) - (0.4105 NTF) + (0.2961 HRT)</td>
<td>40.17%</td>
</tr>
<tr>
<td>Total Hip</td>
<td>T-score = - 1.7902 + (0.0448 Weight) - (0.0324 Age) - (0.4756 NTF) + (0.3175 HRT)</td>
<td>46.80%</td>
</tr>
<tr>
<td></td>
<td><strong>QUS</strong></td>
<td></td>
</tr>
<tr>
<td>Lumbar Spine</td>
<td>T-score = - 4.3986 + (0.0493 BUA)</td>
<td>32.0%</td>
</tr>
<tr>
<td>Femoral Neck</td>
<td>T-score = - 3.8354 + (0.0407 BUA)</td>
<td>38.0%</td>
</tr>
<tr>
<td>Total Hip</td>
<td>T-score = - 3.5697 + (0.0453 BUA)</td>
<td>41.2%</td>
</tr>
<tr>
<td></td>
<td><strong>Combination of Questionnaire Responses and QUS</strong></td>
<td></td>
</tr>
<tr>
<td>Lumbar Spine</td>
<td>T-score = - 5.3457 + (0.0354 BUA) + (0.0281 Weight) - (0.6112 NTF) + (0.3258 HRT)</td>
<td>41.12%</td>
</tr>
<tr>
<td>Femoral Neck</td>
<td>T-score = - 21.3800 + (0.0117 CUBA VOS) + (0.0394 Weight) - (0.0150 Age) - (0.2917 NTF)</td>
<td>50.28%</td>
</tr>
<tr>
<td>Total Hip</td>
<td>T-score = - 25.2570 + (0.0142 CUBA VOS) + (0.0472 Weight) - (0.3247 NTF) - (0.0146 Age)</td>
<td>60.26%</td>
</tr>
</tbody>
</table>
3.3. Results

(a) Questionnaires Responses Model

(b) QUS Parameters Model

(c) Combination Models

Figure 3.2: ROC analyses based on models generated using stepwise regression (see Table 3.5).
Table 3.6: Sensitivity and Specificity of the models generated using stepwise regression

<table>
<thead>
<tr>
<th>DXA Site</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Questionnaire Responses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar Spine</td>
<td>0.92</td>
<td>0.32</td>
<td>0.25</td>
<td>0.94</td>
</tr>
<tr>
<td>Femoral Neck</td>
<td>0.91</td>
<td>0.44</td>
<td>0.21</td>
<td>0.97</td>
</tr>
<tr>
<td>Total Hip</td>
<td>0.91</td>
<td>0.66</td>
<td>0.22</td>
<td>0.99</td>
</tr>
<tr>
<td><strong>QUS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar Spine</td>
<td>0.93</td>
<td>0.49</td>
<td>0.29</td>
<td>0.95</td>
</tr>
<tr>
<td>Femoral Neck</td>
<td>0.91</td>
<td>0.76</td>
<td>0.33</td>
<td>0.99</td>
</tr>
<tr>
<td>Total Hip</td>
<td>0.91</td>
<td>0.73</td>
<td>0.45</td>
<td>0.98</td>
</tr>
<tr>
<td><strong>Combination of Questionnaire Responses and QUS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar Spine</td>
<td>0.90</td>
<td>0.49</td>
<td>0.29</td>
<td>0.95</td>
</tr>
<tr>
<td>Femoral Neck</td>
<td>0.91</td>
<td>0.79</td>
<td>0.42</td>
<td>0.98</td>
</tr>
<tr>
<td>Total Hip</td>
<td>0.91</td>
<td>0.84</td>
<td>0.33</td>
<td>0.99</td>
</tr>
</tbody>
</table>

The multivariate equations used for the calculations of these values are those from Table 3.5

3.3.8 Simplified Models

The simplified versions of the stepwise regressions are presented in Table 3.7. The AUC values and specificities of these new tools are only very slightly different from the original models. For the models using only questionnaire responses the AUC and specificity were 0.79 (0.71-0.87) and 0.28 for the lumbar spine, 0.85 (0.77-0.92) and 0.45 for the femoral neck, and 0.85 (0.76-0.93) and 0.68 for the total hip. For the combination models the values were 0.81 (0.74-0.89) and 0.44, 0.91 (0.87-0.96) and 0.78 and 0.91 (0.87-0.96) and 0.79. The ROC curves for these models are shown in Figure 3.3.
3.4 Discussion

The good to excellent AUC values and the high specificities of the simplified models suggest that a knowledge of a person’s risk factors and a simple QUS measurement may be a very good means of screening for osteoporosis. This is especially noticeable for the femoral neck and total hip. With a sensitivity set to at least 90%, the specificities were 78% and 79%, which are very impressive. If these tools were used in a clinical setting they could help by correctly selecting those who are not at risk of osteoporosis and suggest they be reassessed at a later date. This would drastically reduce the numbers of unnecessary scans and ensure that those at risk are prioritised.

The most important risk factors selected by the stepwise regression (age, weight, history of non traumatic fracture and history of HRT) agree with those selected by other authors. Age and weight have consistently been chosen as the two most influential indicators of low bone mineral density. They appear in risk indices for Asian [Koh et al., 2001], European [Sedrine et al., 2002] and North American [Lydick et al., 1998, Cadarette et al.,

<table>
<thead>
<tr>
<th>DXA Site</th>
<th>Model</th>
<th>Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar Spine</td>
<td>(Weight ÷ 10) - (Age ÷ 10) - (2 × NTF) + (2 × HRT)</td>
<td>3.05</td>
</tr>
<tr>
<td>Femoral Neck</td>
<td>(Weight ÷ 10) - (Age ÷ 10) - (NTF) + (HRT)</td>
<td>1.15</td>
</tr>
<tr>
<td>Total Hip</td>
<td>(Weight ÷ 10) - (Age ÷ 10) - (NTF) + (HRT)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DXA Site</th>
<th>Model</th>
<th>Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar Spine</td>
<td>(BUA ÷ 10) + (Weight ÷ 10) - (2 × NTF) + (HRT)</td>
<td>13.65</td>
</tr>
<tr>
<td>Femoral Neck</td>
<td>(VOS - 1400) + (3 × Weight) - (Age) -(25 × NTF)</td>
<td>278</td>
</tr>
<tr>
<td>Total Hip</td>
<td>(VOS - 1400) + (3 × Weight) - (Age) - (25 × NTF)</td>
<td>250</td>
</tr>
</tbody>
</table>

Table 3.7: Simplified forms of stepwise regression
3.4. Discussion

(a) Simplified Questionnaires Responses Models

(b) Simplified Combination Models

Figure 3.3: ROC analysis based on the simplified models. The curves are generated using simplified stepwise regression from Table 3.7.

The most impressive, and reassuring, result was the final group of risk factors chosen by the stepwise regression. They are the same as those previously selected for another European population. Sedrine et al. [2002] attempted to develop a very simple tool, OSIRIS, for quantifying risk for postmenopausal, Belgian women. They selected age, weight, non-traumatic fracture and HRT as the most significant indicators of low density. There are, however, a number of subtle differences between OSIRIS and the current proposed indices. The first of these is the predicted BMD site. For OSIRIS, the BMD regression models were
3.4. Discussion

compared to the lowest BMD T-score from the spine or hip. While this approach may help
to create a more generalised tool, some specificity may be sacrificed. For this work it was
deemed more appropriate to develop separate tools for each site. Although this means that
there are three formulae to apply, it is still relatively straightforward.

A second point to note is the different age range of the samples. Sedrine and cowork-
ers dealt with an older sample; a mean age of 67.1 ± 5.2 years with a minimum age of 60
years. This is compared to 59.7 ± 10.8 years for this sample. This leads the author to be-
lieve that such tools can be used across a larger age range, without reducing effectiveness.
Considering that the mean age at menopause in this group was 44.8 years, a tool designed
for those from 60 onward would be of little use.

All in all, the overall agreement in the selected determinants of low density in these
newly developed tools and other tools reaffirm their importance. It is possibly unsur-
prising that OSIRIS and these tools are so similar given that they were both created for
postmenopausal, European, Caucasian populations. The partial agreement with ORAI and
SCORE may also be explained, in part, by the North American, Caucasian populations
used in their creation. One point that Cadarette et al. [2000] evaluated but has not been
considered here is that of ethnicity. Many studies have presented differences in mean den-
sity values for various ethnic groups. This was not an issue with the present work because
all volunteers were White British.

As was stated above, there are a number of other risk assessment tools that have been
created for postmenopausal women. It was decided to calculate these indices for this
sample in order to compare their efficacy. OST was computed first and compared to the
BMD at the femoral neck (as per the original specification) [Koh et al., 2001]. Specificity
was 0.45, which was identical to specificity of the model created here (for the femoral neck) to discriminate between osteoporotic and normal. It is also interesting to note that the OST tool, which is based on just age and weight and was developed for an Asian population, performs as well a model which also considers non-traumatic fractures and the use of HRT.

The OSIRIS tool was then applied. This was done in accordance with the original author’s protocol. This meant only women between the ages of 60 and 80 years were included ($n = 104$), and results were compared to lowest available DXA T-score. A specificity of 0.36 was derived. This is in line with the 0.33 and 0.44 values found here for the lumbar spine and the femoral neck, but less than the 0.66 found for the total hip. The choice of tool is therefore dependent on the site the health care professional is most interested in. In work carried out by Nevitt et al. [1994], hip BMD was seen to be the best predictor of osteoporotic fracture at the hip. With each standard deviation decrease in BMD showing the highest increase of relative risk of fracture. Similarly, Cummings et al. [2002] showed that changes in hip and spine BMD resulted in similar changes in the risk of lumbar fracture. This suggests that risk assessment tools for the femoral neck and total hip from the current work may be more effective as a screening tool than OSIRIS. However, if for any reason a DXA measurement is not possible at the proximal femur, and lumbar scanning is carried out instead, then it appears either tool would work equally well.

The SCORE and ORAI indices are not directly comparable with the current tools because they were initially designed to predict low BMD (T-score $\leq -2$), as opposed to the traditional T-score $\leq -2.5$. For this reason, no analyses were calculated using these assessment tools.
3.4. Discussion

The significant relationships between the QUS variables and the DXA measurements comply with previously published work. Whilst investigating the correlation between QUS at the heel and DXA scores for a Belgian population, Boonen et al. [2005] documented similar values. The stiffness index was compared with BMD values from the lumbar spine a coefficient of 0.48 was found. Although, the parameters are generated slightly differently, they are comparable. A more direct comparison can be made with the work of Cook et al. [2005], who found correlation coefficients which are similar to those found for this population.

The correlation coefficients found for the Sunlight Omnisense in the present study are less than those found in previous work using this device. Knapp et al. [2001] found values of up to 0.48 between the speed of sound at the phalanx and the BMD at the femoral neck. However, these values were calculated using both pre- and postmenopausal females. The significantly higher BMD and SOS values of the premenopausal sample led to, in this author’s opinion, exaggerated results. If only the postmenopausal sample were used in the computation of the coefficients, it is expected that these would be much less impressive.

The good to excellent correlation coefficients observed between the DXA measurement sites are expected. It is also expected that the greatest correlation is between the femoral neck and the total hip, given that there is some overlap in the regions of interest in the scans used for calculating BMD at these sites. It is also expected that two sites that are anatomically close would experience similar rates of bone turnover because they undergo similar stress cycling.

Even though the lumbar spine and hip measurements have both proved to be good predictors of osteoporotic fracture, not all of the variability of the BMD measurements
of one, is explained by the other. Therefore, it is unrealistic to expect any measurement, regardless of the technique, from any other skeletal site to predict low BMD perfectly. This is one of the greatest supporting arguments why the assessment tools from this study were not condensed into a single algorithm, as has been done previously. Instead, it was acknowledged that a medical practitioner may be more interested in a particular site.

The improved specificity of the above tools, compared with that found for a single model, is also an important issue with regard to reducing the strain on available DXA services. For example, focusing on the total hip model, the high specificity would mean that 79% of the healthy individuals sent for scanning, which represents 169 of the 235 in total, could instead be selected for reassessment at some point in the future. This would indeed result in the prioritisation of those at risk and more efficient use of resources. This specificity is considerably greater than that found when other tools were used on similar populations.

Is it more important to detect those with the condition, even if healthy individuals are misdiagnosed as diseased? Or, it is more beneficial to remove as many people as possible from further investigation, with the risk that some diseased people are denied treatment? Decisions about the most important scenarios to detect were made. A cut-off that ensured a sensitivity of 90% was decided upon for this work. The main morbidity involved is a fracture of the hip (and spine) which is very uncomfortable and very dangerous, with many people dying even after hip replacement surgery [Cummings and Melton, 2002]. Therefore it was believed that it is better to spend money on the extra DXA scans. This also raises the question ‘Why not set the sensitivity to 100%?’ The problem with making a tool with very high sensitivity is that specificity suffers. One might arrive at a position
3.5. Conclusions

where every diseased individual is selected, but very few people are actually excluded. Therefore, the sensitivity of 90% was seen as the most appropriate balance.

3.5 Conclusions

The work presented here has shown that the judicious selection of risk factors collected from questionnaires can be used to reduce the number of DXA scans performed on healthy individuals. A simple cumulative system can help predict those at highest risk. Adding QUS data to these significantly improves the accuracy of tools. The ease of use and inexpensive nature of both of these tools would suggest that the future of pre-screening for osteoporosis lies in using both in tandem.
Prototype Design

Complexity is one of the great problems in environmental design

Christopher Alexander

The previous chapter has shown that the presence, or lack of, certain risk factors along with QUS measurements allow for categorisation of people based on their risk of osteoporosis. The next step was to attempt to optimise QUS techniques to determine if the utility, as a screening tool, could be improved for a Caucasian population. This chapter outlines the design process and initial testing of a prototype device to scan with ultrasound.

4.1 Which site to choose?

The goal at the outset was to improve the diagnostic ability of QUS techniques. With this in mind, the first issue was choosing a site to measure. The most studied QUS measurement sites are the calcaneus, the distal radius and the proximal phalanx. However, the capitate,
4.1. Which site to choose?

Clavicle, metacarpal, patella, thoracic spine and tibia have all been investigated as possible scanning sites with various degrees of success.

Ideally, the site chosen for this work would have a track record of good correlation with BMD T-score at clinically relevant sites, regardless of the exact parameter measured. It also needed to be easily accessible and would allow for repeatable measurements. For this tool to be successful in the environment it is expected to perform in, a general practitioner’s practice for example, this is very important. It is envisaged that a person could receive a quick scan with very little preparation.

After examining the literature available on the topic and consultation with a rheumatologist in The Great Western Hospital, Swindon, the proximal phalanx was chosen as the most suitable site.

Published research has shown that speed of sound measurements along and through the phalanx have promising relationships with BMD T-scores at the lumbar spine and hip. They have also been seen to have the ability to discriminate between those with and without osteoporotic fracture. The UBPI, an index based on parameters such as the speed of sound, energy and amplitude of the first arriving wave, has also been shown to correlate with axial bone density.

The finger is also very accessible. It can be scanned very comfortably, with minimal preparation time or effort. Furthermore, it requires no clothes are removed. It is very rarely damaged, so results are in no way affected by previous fractures. Although some people may have swelling of the joints due to arthritis, this does not inhibit transducer contact with the diaphysis of the phalanx.

This was seen as sufficient evidence that changes were happening at the finger that
were in line with changes at more metabolically active sites, and that it would provide a comfortable, open, easy scanning site.

4.2 Design Constraints and Requirements

There are a number of constraints and requirements that needed to be satisfied. These are listed here.

**Scan across the finger** One of the most fundamental requirements for the device is to allow for scanning across the proximal phalanx, in a medio-lateral direction. This is to allow for scanning of bone with the least amount of soft tissue between transducer and bone, reducing the possibility of excessive attenuation or scattering of the wave. Also, the relatively flat sides of the proximal phalanx would allow for easy positioning of the transducers.

**Allow accurate transducer placement** In order to scan individuals in a standardised manner, accurate marking and scanning of the region of interest is required. To achieve this, it was decided to make the device with a platform to rest the hand upon during scanning. This was envisaged to be more stable than a hand-held device, thus reducing possible error due to relative movement of scanner and finger. Also, a pad which constrains the finger in a vertical axis was also needed. This was designed so that the finger could be rested against it by applying a light upward force.

**Adjustable** The device needed to be adjustable such that it is possible to align every finger with the same angle to the transducer. This was to reduce the potential for error due to misalignment. A hinged mechanism was designed to enable rotational correction.
Open design. The population most at risk of osteoporosis, and which this device is aimed, is postmenopausal women. In order to facilitate scanning of this population there are a couple of considerations regarding the scanning site which need to taken into account. Firstly, some of those to be scanned may also have arthritis at the finger joints. This will mean inflamed joints that need to be avoided when scanning. To combat this, an open design was adopted. Another issue was the fact that many individuals will have reduced mobility of the finger. Therefore the device was designed so that minimal movement and positioning was required on the part of the person being scanned.

4.3 Prototype Design

With the above constraints and requirements accounted for, a relatively straightforward setup was decided upon. This consisted of a pair of collinear ultrasound transducers connected to a linear variable differential transducer, allowing for the transmission and collection of the ultrasonic wave, with simultaneous measuring of the separation distance. This was then attached to a panel which was hinged to the base platform, upon which individuals could rest their hand. The envisaged prototype can be seen in Figure 4.1. A complete set of mechanical drawings of the prototype can be viewed in Appendix F.
Figure 4.1: Three dimensional CAD drawing of prototype. The transmitter (a) and receiver (b) are collinear. The plunger mechanism (c) allows for control over the separation of the transducers. The pad to control the position of the finger in the vertical axis (d) is visible. The height of this pad can be adjusted by screwing it up or down. The LVDT is hidden under the housing (e).

4.4 Software Used

The software used was provided by McCue Plc (Southampton, UK). With this software, the parameters of the measurement can be selected, such as the desired number and time interval between scans. Certain thresholds required can also be set from this screen, such as the trigger level used to calculate time of flight and time to stop collecting information. Finally, there is a section where the user can save the results file generated, the received waveform and the data used to calculate the BUA.
4.5 Testing of Prototype

When the prototype had been built, it was decided to test it on a number of members of staff at Cranfield University in order to see if the device could be used easily and if it was comfortable for those being scanned. A sample of men and women between the age of 22 and 65 years of were scanned. The scans were completed as if they were being performed in a clinical setting.

From an operator point of view the prototype performed well. Individuals could be positioned easily and accurately. The only issue encountered was the loose sliding of the plunger which closed the transducers. This was easily remedied by tightening this part of the device.

Those scanned were asked for feedback about the scan, especially about how simple it was to position their finger initially and hold it in that position. All those scanned remarked that both positioning and remaining still were hampered by the pad designed to prevent movement in the vertical axis. This can be seen in Figure 4.2.

It was decided to replace this pad with a cushioned block on which individuals could rest their finger. The theory was that it would be easier for people to rest their finger on a block and bring the scanner into position, than to move the finger into position and keep applying a constant force on the positioning pads.

After this modification, the same group of individuals were scanned a second time. All participants agreed that second scan was more comfortable, felt more secure and required much left effort than the first.
4.6 Conclusions

Figure 4.2: All volunteers experienced difficulty holding their finger against the upper pad, whilst being scanned. In this picture the finger has already begun to slide out of position (within the red circle).

4.6 Conclusions

A prototype ultrasound scanning device had been designed, manufactured and tested for usability. Initial tests showed that the device was easy to operate and comfortable. It was now ready to be tested in a research environment.
Chapter 5

In vivo Testing of the Proximal Phalanx

For each of us who appear to have had a successful experiment there are many to whom their own experiments seem barren and negative

Melvin Calvin

There are a number of ultrasound measurements that are used to predict axial density. Over the past couple of decades, the list of parameters for the finger has increased. While these may have been introduced to aid clinicians make informed choices, the choice of the appropriate measurement may be difficult. The developed prototype would allow for the collection of these parameters, along with a number of new ones. This chapter describes the process of collecting these data and comparing it to density to determine which method performs best.
5.1 Introduction

A previous chapter (Chapter 3) demonstrated that ultrasound measurements along with known risk factors could be used to select patients most requiring DXA screening and possible treatment. QUS at the calcaneus showed the greatest promise, remaining significant even when the questionnaire responses were accounted for. However, only a small number of QUS inputs were used. There are other which were not included that may have performed better.

QUS at the finger has for a long time been an attractive site to scan with ultrasound devices. It is easy to access, not covered by a great deal of soft tissue and has relatively flat sides. This has led to the development of many ultrasound parameters believed to reflect the condition of the skeleton [Wüster et al., 2000].

These parameters were not collected for the sample of the previous chapter (Chapter 3) because the technology was not available to do so. However, because the measurements proposed for QUS at the phalanx seemed to perform so well in published work, it would be shortsighted to completely exclude these. The prototype device was designed such that every waveform could be collected. Post processing would then allow the calculation for any number of parameters. With T-Scores of the same individuals, the usefulness of these parameters can be determined.

Also, the collection of data for a large cohort would allow for possible validation of the assessment tools presented earlier. Therefore, volunteer data required to calculate the risk indices was also recorded.
Table 5.1: Demographics of Sample from the Great Western Hospital

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (± SD) or Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>57.6 (± 12.2)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>71.4 (± 16.1)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>164.9 (± 8.1)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.37 (± 5.7)</td>
</tr>
<tr>
<td>Current Smoker</td>
<td>18 (10.5%)</td>
</tr>
<tr>
<td>Age at Menarche (Years)</td>
<td>13.1 (± 1.7)</td>
</tr>
<tr>
<td>Age at Menopause (Years)</td>
<td>46.1 (± 7.4)</td>
</tr>
<tr>
<td>History of Non Traumatic Fracture</td>
<td>19 (11.0%)</td>
</tr>
<tr>
<td>Use of Hormone Replacement Therapy</td>
<td>73 (42.9%)</td>
</tr>
</tbody>
</table>

Non Traumatic Fracture was defined as a fracture caused as a result of minimal trauma based on the questionnaire responses.
Hormone Replacement Therapy was assigned if the subject had been using it for ≥ 1 year and treatment began before the age of 60.

5.2 Methods

5.2.1 Sample

An initial cohort was gathered from a DXA scanning clinic in the Great Western Hospital (Swindon, UK). Ethical approval was granted for the study by the ethics committee in the hospital prior to commencement of testing. All volunteers were sent an information sheet (Appendix C) along with their appointment notification. This information sheet explained the study hypothesis and the procedure involved, should they choose to participate. All volunteers were given the opportunity to ask any questions with the main researchers before any testing took place. Written informed consent was collected at the time of scanning. The demographics of the sample (n=123) can be seen in Table 5.1.
5.2.2 DXA

All volunteers underwent DXA scanning as part of their visit to the clinic. Bone mineral density measurements were taken at the lumbar spine, femoral neck and total hip. All femoral neck and total hip scans were taken of the left hip except where hip fractures or hip replacements were present. All DXA results are given as T-Score values.

5.2.3 Questionnaire Data

Each volunteer was given a questionnaire to complete (Appendix A) pertaining to activity, lifestyle, medical history, diet and reproductive history. Advice was available in the form of a brief discussion with the main researcher if necessary. Weight and height details was also taken at this time.

5.2.4 Quantitative Ultrasound

QUS measurements were taken using three machines, varying in their design and measurement site. Two commercially available devices were used. The first was the Sunlight Omnisense (Sunlight Medical, Rehovot, Israel) which measured the axial speed of sound at the distal radius (SOS$_{DR}$) and the third proximal phalanx (SOS$_{PP}$). The CUBA Clinical was used to measure through velocity (VOS) and broadband ultrasound attenuation (BUA) at the calcaneus. The developed prototype device was also used which measures the through velocity at the second proximal phalanx (VOS$_{PP}$). The prototype was used to measure the Time of Flight Velocity (VOS$_{TOF}$), Energy of the First Wave (E$_{FW}$), Velocity of First Peak (VOS$_{FP}$), Velocity of the Slow Wave (VOS$_{SW}$) and Time Frame (TF). Figure
5.2. Methods

Figure 5.1: This figure shows how the QUS variables are calculated. The Time of Flight Velocity, Fast Wave Velocity, and Slow wave Velocity are calculated based on the distance across the digit and the crossing times as demonstrated. The Energy of the First Wave is represented by the shaded area. Finally, the Time Frame between the fast and slow wave is also visible.

5.1 show how these parameters are calculated. Measurements were taken at 60 and 70% of the length of the proximal phalanx of the second digit of the non-dominant hand.

Aquasonic® Clear Ultrasound Gel (Parker Laboratories Inc, Fairfield, N.J.) was used to ensure coupling between sites of measurement and transducers. The commercially available devices were quality checked on each day of scanning using phantoms provided with the systems. The prototype device was quality checked using manufactured phantoms.
5.2.5 Validation of Risk Factor Indices

The results of all questionnaires were input into a spreadsheet. Those with secondary causes of osteoporosis were not included. Those with essential information missing from their questionnaires were not included as accurate scores could not be calculated. The index scores were calculated for $n = 121$ individuals using only the responses and $n = 78$ using questionnaire responses and QUS values, as per the published equations and cut-offs [Minnock et al., 2008].

5.3 Results

5.3.1 DXA

The DXA results were within the range for a postmenopausal sample. The comparison of the values from each site are presented in Figure 5.3. The correlation between the lumbar spine and femoral neck ($R = 0.722, P < 0.001$) and lumbar spine and total hip ($0.721, P < 0.001$) were comparable. The correlation between the total hip and femoral neck was greater ($R = 0.891, P < 0.001$).

5.3.2 QUS Devices

The calculated coefficient of correlation between the commercial QUS devices and the DXA measurement sites can be seen in Table 5.2. BUA at the calcaneus had the highest correlation with all T-scores. $SOS_{DR}$ was not significantly correlated to the T-score at any site.
5.3. Results

(a) Femoral Neck versus Lumbar Spine

(b) Total Hip versus Lumbar Spine

(c) Total Hip versus Femoral Neck

Figure 5.2: T-scores form the lumbar spine, femoral neck and total hip plotted against one another. The correlation coefficient is greatest between the total hip and femoral neck (R = 0.891, P < 0.001).
5.3. Results

Table 5.2: Results of simple regression between commercial QUS devices and DXA T-scores. Results are given for lumbar spine, femoral neck and total hip

<table>
<thead>
<tr>
<th>QUS Variable</th>
<th>Lumbar Spine</th>
<th>Femoral Neck</th>
<th>Total Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>VOS</td>
<td>0.226 P &lt; 0.05</td>
<td>0.326 P &lt; 0.005</td>
<td>0.333 P &lt; 0.005</td>
</tr>
<tr>
<td>BUA</td>
<td>0.273 P &lt; 0.05</td>
<td>0.407 P &lt; 0.001</td>
<td>0.375 P &lt; 0.001</td>
</tr>
<tr>
<td>$SOS_{PP}$</td>
<td>0.249 P &lt; 0.01</td>
<td>0.259 P &lt; 0.01</td>
<td>NS NS</td>
</tr>
</tbody>
</table>

The VOS$_{TOF}$ was significantly correlated to the DXA T-scores of the lumbar spine and femoral neck. However, the correlation coefficients were low (Figure 5.3). The other proposed QUS parameters ($E_{FW}$, VOS$_{FP}$, VOS$_{SW}$ and TF) were not significantly correlated to the DXA T-scores at any site.

5.3.3 Validation Study

Plots of the measured DXA T-scores against the risk indices can be seen in Figure 5.4. The sensitivity and specificity values were computed using the cut-off thresholds used in the published work and are presented in Table 5.3. The sensitivity was greater than 90.0% for all indices. The specificity of both the hip risk indices were higher, 57.4% at the femoral neck and 76.5% at the total hip, than that at the lumbar spine, 24.1%.

For the models that include a QUS variable, the sensitivity values were all less than 90% for the proposed cut-off. This is below the acceptable level set out at the beginning of this work.
5.4 Discussion

The correlation between the DXA values and the QUS parameters from the commercial devices are within the normal range for a British population. The QUS at the finger however appeared to perform however less impressively than previously thought. The VOS$_{TOF}$ was the only parameter that appeared to have a significant relationship with the DXA values. Unfortunately this was much less than for published work (Chapter 2). There are two very

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**Figure 5.3:** The weak correlations between the TOF Velocity (VOS$_{TOF}$) and the T-scores of the lumbar spine and femoral neck are presented. There was no significant correlation between the TOF Velocity and the T-scores of the total hip.
Figure 5.4: T-scores form the lumbar spine, femoral neck and total hip are plotted against the calculated risk indices. The horizontal dashed lines represent a T-score of -2.5.
Table 5.3: Performance of risk indices with a validation study.

<table>
<thead>
<tr>
<th>Calculated Index</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar Spine</td>
<td>100.0</td>
<td>24.1</td>
</tr>
<tr>
<td>Femoral Neck</td>
<td>92.3</td>
<td>57.4</td>
</tr>
<tr>
<td>Total Hip</td>
<td>100.0</td>
<td>76.5</td>
</tr>
</tbody>
</table>

important differences between the samples that must be considered.

Wüster et al. [2000] investigated the age related changes that were observed for velocity. There are changes in axial density that occur with aging. It is these very changes that have led to the definition of osteoporosis. However, assuming that these changes may be related to changes in QUS parameters at appendicular sites, or indeed that using one, the other may be predicted is not ideal. Indeed, Faulkner et al. [1999] have reported the difficulties associated with this type of assumed link. The authors measured the changes in DXA and QUS around the body, and found that the decrease in measurements was not uniform. Therefore, depending on the measurement type, many individuals were misclassified. This is the reason that the all results here are compared to density and not age.

The second major difference between this study and others is the fact that only postmenopausal women were investigated. In the past, when QUS parameters were being investigated for changes with aging, authors tended to look at people from 20 years to 80 years. Almost always, great difference were noted between the groups in their twenties and thirties and those much later in life. These decreases allowed for the calculation of the annual rate of change. However, this present sample was all postmenopausal, the range of ages was much smaller (closer to 30 years). This may have meant that the difference between the best and worst values were much less. This appears to lead to the situation
where these measurements may not be used to predict changes in axial density.

The assessment tools described in Chapter 3 were tested using responses provided by the volunteers. The simple tools using only the risk factors proved very useful, with high specificity values. In fact, the tools for predicting T-Score at the femoral neck and total hip actually outperform the original expectations.

The tools that included QUS at the calcaneus did not match the performance of the development study, with sensitivity values less than 90% at all sites. This does not mean that these are incorrect, but rather the cut-off values that were suggested were not appropriate. Further work is required in order to determine the ideal threshold that ensures a high sensitivity for these.

5.5 Conclusions

Validation of the very simple assessment tools have shown that they are indeed an excellent means of prioritising those most in need of DXA services. The addition of QUS however did not increase the accuracy of these tools. Further work is required to select the appropriate thresholds for use. QUS at the finger was not able to predict T-Scores at the most relevant clinical sites. Improvement of these parameters or examination of novel measurements is necessary if bone quality is to be determined from simple ultrasonic investigation of the phalanx.
Chapter 6

Modelling and Simulations: In vivo

There’s two possible outcomes: if the result confirms the hypothesis, then you’ve made a discovery. If the result is contrary to the hypothesis, then you’ve made a discovery

Enrico Fermi

The design and manufacture of the prototype device would allow for the collection of ultrasonic data. Whilst recognised parameters could be measured with ease, novel and more applicable data could also be recorded. In order to test a new ultrasound variable, it was deemed necessary to test the basic principles on a smaller sample first. To investigate the ultrasonic parameters and their dependencies on the density and morphology of the scan site, it was decided to simulate the scenario. This way the geometries, material properties and input signal could be controlled and the effect on the waveform could be monitored.
6.1 Introduction

The proposition of optimising ultrasound scanning for the British population can be tackled in a variety of ways. Of these, two stand out as potentially the most viable options. The first is to look at the current techniques used, find the elements that affect the accuracy and precision of the measurements, and reduce or remove these. One assumption of this approach is that the theory of the measurement process is completely understood. For example, a person’s height will reflect how tall they are. Furthermore, more accurate and precise means of calculating height will enable better measurements.

The author feels that the method of optimisation of speed of sound measurements is not appropriate. The reason for this is the lack of agreement over what the speed of sound measurements are a function of. Many investigators have suggested that the velocity measurements are suitable for forecasting the likelihood of osteoporosis because they reflect changes in density and elasticity [Lee et al., 1997, Hans et al., 1999b, Prevrhal et al., 2001]. The close relationship between the density and the elasticity in bone, as described earlier, may allow us to assume that it would be foolish to investigate either of these entirely independently. Thus predicting one by means of ultrasound, the other could be calculated. This may be the case when measuring large, geometric, perfectly isotropic samples. However, the human skeleton does not provide such sites for investigation. This may explain why in the above studies the variability of the velocity was not completely explained by either the density or the elasticity.

Njeh et al. [1999b] studied the effects of sample thickness on axial velocity of perspex and bovine bone. They noted that the measured velocity depended on thickness up to a certain threshold, and thereafter remained constant. They proposed that the velocity being
measured was the phase velocity of flexural waves, as phase velocity depends on thickness (indirectly, via the radius of gyration). Therefore, there is confusion over what affects these velocity measurements and what is being predicted when velocity measurements are taken. Does it depend on density or thickness, or a combination of these two? Indeed, Sievänen et al. [2001] have demonstrated significant correlations between velocity and density and between velocity and cortical thickness in vivo at the tibia. For these reasons, it was believed that optimising velocity measurements was not the most appropriate way to proceed.

The second approach is to look at the manifestations of osteoporosis and attempt to predict these using quantitative ultrasound. The author felt that this method showed the most promise. The reason is that there is more scope for investigating what is thought to be important, and not what has been proposed in the past.

The manifestations of osteoporosis in cortical bone, the type of bone present in the diaphysis of the phalanx, are varied: decreased density [Boonen et al., 2005], increased porosity [Marcus, 1996], trabecularisation of the endocortical surface [Keshawarz and Recker, 1984] and thinning of the cortex [Grampp et al., 1997]. The development of large pores and trabecularisation may be localised, and would therefore make meaningful predictions based on these parameters difficult. As density depends on porosity, it too may prove over optimistic or pessimistic depending on the exact site and pathway interrogated. Cortical thinning, on the other hand, is thought to progress at a relatively uniform rate around the finger. It was therefore decided to attempt to monitor the changes in the thickness of the cortex.

This begs the question of how to determine and monitor cortical thinning. Cadossi
and Cane [1996] looked at the effect of drilling in the medullary cavity on the waveform that interrogates pig phalanges. They noted that as the medullary cavity was expanded the wave changed shape. More specifically, total normalised energy decreased, and the distribution of energy according to various energy velocities changed. Although the authors propose that fast arriving signal originates from the cortex, they offer little explanation as to the rest of the waveform. This is understandable, given that it is not possible to view the ultrasonic wave in transit. This was the case until researchers began to simulate the process. When Barkmann et al. [2000] presented their findings on simulation work, they dismantled the waveform by the pathways taken through the finger. They documented three main paths. The first was the fast arriving signal that travels through the cortex. The second is the part of the signal that crosses the cortex into the medullary cavity before exiting via the cortex on the other side. The final part of the signal is that which the crosses the finger via the soft tissue. The three separate waves can be seen in Figure 6.1.

![Figure 6.1](image_url)

**Figure 6.1:** The pathways of the ultrasonic wave through the phalanx are visible when the simulation software is frozen at different times. The ultrasonic wave may travel through the cortex (a), the cortex and the medullary cavity (b) or the soft tissue (c). These waves arrive in this order at the receiving transducer.

By using this theory to explain the collected waveforms, it was postulated that each individual part of the waveform reflects changes in the structure of the finger. It also allows the possibility of dividing the wave into logical partitions, instead of the more arbitrary
6.2 Methods

6.2.1 Sample

The study sample comprised 14 volunteers (8 females and 6 males) from the staff and students of the Alsager campus of Manchester Metropolitan University. Ethical approval was granted by the ethics committee of the university before the study commenced (Appendix D). All volunteers were given an information sheet explaining the hypothesis of the study and what was involved, should they take part (Appendix E). Written consent was obtained.
Table 6.1: Demographics of Sample for in-vivo Testing

<table>
<thead>
<tr>
<th>Variable</th>
<th>Female</th>
<th>Male</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>47.1 (26–64)</td>
<td>46.0 (24–63)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.1 (± 20.4)</td>
<td>84.8 (± 23.9)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.63 (± 0.07)</td>
<td>1.77 (± 0.05)</td>
</tr>
<tr>
<td>BMI (kg/m^2)</td>
<td>25.6 (± 7.3)</td>
<td>26.7 (± 6.4)</td>
</tr>
</tbody>
</table>

before inclusion in the study. Participants were able to exclude themselves at any time.

The sample demographics can be seen Table 6.1.

6.2.2 Questionnaire

Before any scanning took place, each volunteer completed a questionnaire relating to physical activity, diet, lifestyle, medical and reproductive history (Appendix A). There was an opportunity to clarify any queries with the researcher if required. Special attention was paid to the section relating to medical history and any medications been taken. No volunteers were seen to have any conditions or be taking any medications known to affect bone metabolism or which may lead to secondary osteoporosis.

6.2.3 pQCT Measurements

pQCT was used to measure the cortical area and cortical density along the proximal phalanx of the second digit of the non-dominant hand. Measurements were taken using a STRATEC XCT-2000 pQCT ® (Stratec, 75217 Birkenfeld, Germany). The resolution of the device is 0.2 mm. Measurements were taken at sites corresponding to 50, 60 and 70% of
the total length of the phalanx. The scanned images (Figure 6.2) were used to generate the input geometries required for the Wave2000 simulation package.

6.2. Methods

Wave2000 (CyberLogic Inc, New York, NY, US) was used to simulate the passage of the ultrasonic waves through the proximal phalanges. In order to use the images obtained from the pQCT, some manipulation was required. Firstly, soft tissue needed to be disregarded. This was accomplished by removing all tissue with a pQCT density below the threshold density for cortical bone (710 mg HA cm$^{-3}$). The remaining tissue was assumed to be a cortical ring surrounding a medullary cavity. This structure was then modelled in an idealised finger (16 mm $\times$ 16 mm as per Figure 6.3).
Figure 6.3: The cortical bone that remained after the soft tissue is removed can be seen. The black area represents the medullary cavity. Darker areas in the cortical bone represent regions of higher density.

Two sets of simulations were carried out. The first assigned all bone present the default material properties of ‘Bone, human cortical’ from the library of materials in Wave2000, hereafter referred to as simple bone. The second calculated the material properties based on the pQCT densities, hereafter referred to as complex bone. Areas of similar density, as per the density bands, were set to the same material properties. The densities of hydroxyapatite, collagen and water were assumed to be 3.00 g.cm\(^{-3}\), 1.14 gm.cm\(^{-3}\) and 1.00 g.cm\(^{-3}\) respectively. Using the prediction of \(\rho_{Apparent\,Dry}\) (Equation 6.1) by Keller et al. [1990], tissue density was calculated.

\[
\rho_{Apparent\,Dry} = 0.043 + 1.45 \times \rho_{Ash} \tag{6.1}
\]

These values for tissue density (g.cm\(^{-3}\)) allowed for the prediction of Young’s Modulus (GPa) using the prediction put forward by Snyder and Schneider [1991] (Equation 6.2).

\[
E = 10^{10.59} \rho_{Tissue}^{2.39} \tag{6.2}
\]

With the values for Young’s Modulus, the Lamé coefficients (Equations 6.3 and 6.4)
were calculated, assuming \( \nu = 0.33 \). The Lamé constants are required by the Wave2000 program for any materials to be modelled which are not found in the library of materials.

\[
\lambda = \frac{E(x)\nu}{(1 + \nu)(1 - 2\nu)} \tag{6.3}
\]

\[
\mu = \frac{E(x)}{2(1 + \nu)} \tag{6.4}
\]

The soft tissue surrounding the bone was modelled as 'Sea Water @ 25 deg C', while the tissue within the medullary canal was modelled as 'Fat, pig', both of which are available in the Wave2000 materials library. The transmitter and receiver were represented as transducers on opposite sides of the created geometry such that the ultrasonic wave would travel across the phalanx, much like how it would in real life. These were set to 12.7 mm in length and single pulse of 1 MHz was used as the input signal.

**Time of Flight Velocity**

The simulated time of flight velocity (\( \text{VOS}_{TOF} \)) was computed as per Equation 6.5. For the calculation of this velocity, the velocity of sound through water (\( \text{VOS}_{\text{Water}} \)), the separation between the transducers (\( x \)) and the time difference between a measurement with bone present and without (\( \Delta t \)) are required.

\[
\text{VOS}_{TOF} = \frac{\text{VOS}_{\text{Water}}x}{x - (\Delta t \text{VOS}_{\text{Water}})} \tag{6.5}
\]
6.2. Methods

Proportion of Fast Energy

The proportion of fast to slow arriving energy was calculated. This was done by calculating energy of various parts of the received waveform. A simulation was run with no bone present. This was used to calculate the time of flight through soft tissue. The fast arriving signal was defined as the waveform up to this point and the slow arriving signal was from this point thereafter. These two were integrated to calculate the energy of each respective part. Figure 6.4 shows a waveform after the signal has passed through a geometry with no bone present (a). This was used to determine the slow wave start and end point (the vertical dashed lines). Everything prior to this point was consider to be part of the fast wave. Part (b) of Figure 6.4 shows a rectified sample waveform through a finger. The shaded areas under the curves are the fast wave energy and the slow wave energy respectively. Finally, the proportion of fast to total energy (PRO) was computed.

6.2.5 Frequency Testing

In order to test the effect of frequency on the resultant waveforms, the simple bone models were also run at 0.5, 2.0 and 5 MHz. All other material properties and model parameters, including the duration, remained the same. These repeat tests at different frequencies were carried out on each geometry for all of the participants in the study.
6.2. Methods

(a) Waveform through Geometry

(b) Waveform through Sample Phalanx

**Figure 6.4:** The wave through the geometry with no bone present, Figure (a), was used to determine the start and finish points (the dashed grey lines) of the wave travelling through the soft tissue. These were then used to determine the fast and slow waves, Figure (b), of the rectified wave of samples with bone present.
6.3 Results

6.3.1 pQCT

The pQCT results are presented here. Because the density profiles, changes in geometries with age and manifestations of osteoporosis differ for males and females, the pQCT results are dealt with separately. All future results will combine male and female data.

Cortical Density

For the females in the sample, there appeared to be a quadratic relationship between density and age at each of the measurement sites (Figure 6.5). The $R^2$ values were 0.774 ($P < 0.05$) and 0.828 ($P < 0.05$) at 60% and 50% of the length of the phalanx. The relationship was not significant at 70%, with $R^2 = 0.462$ ($P = 0.21$). Based on the fitted curves, the maximum density is reached in the fifth decade.

No significant relationship, linear or quadratic, was found for the male volunteers.

Cortical Area

No significant relationships were observed between the cortical area and the age for either females or males.

6.3.2 Wave2000 Simulations

The $VOS_{TOF}$ was found to be significantly correlated to the cortical area at each of the investigated sites for the models using simple and complex bone. For the simple bone the correlation coefficients were $R = 0.89$, $R = 0.88$ and $R = 0.89$ (All at $P < 0.001$) for the
6.3. Results

Figure 6.5: Cortical density plotted versus Age at 50, 60 and 70% of the overall length of the proximal phalanx (Data is for females only).

complex bone and R = 0.91, R = 0.90 and R = 0.88 for the complex bone (All at P < 0.001).

VOS\text{TOF} can be seen plotted against cortical area in Figure 6.6.

The PRO measurements were also seen to be correlated to the cortical area. The correlation coefficients were R = 0.87, R = 0.94 and R = 0.88 (All at P < 0.001) for the models using the simple bone. The correlations were lower when complex bone was modelled; R = 0.82, R = 0.80 and R = 0.88 (All at P < 0.01). Figure 6.7 displays PRO plotted against cortical area at each site.

6.3.3 Varying Frequency

Each waveform collected using the simple bone models 0.5, 1.0, 2.0 and 5.0 MHz was plotted. A sample of each frequency for the same individual at the same site is presented
6.3. Results

(a) 50% Simple Bone  
(b) 60% Simple Bone  
(c) 70% Simple Bone

(d) 50% Complex Bone  
(e) 60% Complex Bone  
(f) 70% Complex Bone

Figure 6.6: The above images show the relationship between the time of flight velocity ($V_{\text{OS}_{\text{TOF}}}$) and cortical area. Plots (a), (b) and (c) are for the simple bone, whereas (d), (e) and (f) are for the complex bone.

(a) 50% Simple Bone  
(b) 60% Simple Bone  
(c) 70% Simple Bone

(d) 50% Complex Bone  
(e) 60% Complex Bone  
(f) 70% Complex Bone

Figure 6.7: The above images show the relationship between the proportion of fast to total energy (PRO) and cortical area. Plots (a), (b) and (c) are for the simple bone, whereas (d), (e) and (f) are for the complex bone.
in Figure 6.8. As the frequency increased from 1.0–5.0 MHz the signals become more incoherent. Reflections and scattering caused the received waveform to become less well defined. This makes it impossible to discriminate between the parts of the signal arising from different structures in the finger.

![Waveform Images](image)

(a) 0.5 MHz  
(b) 1.0 MHz  
(c) 2.0 MHz  
(d) 5.0 MHz

**Figure 6.8:** Sample waveforms collected by the receiving transducer for the same individual at 0.5, 1.0, 2.0 and 5.0 MHz. All other properties and parameters were kept constant.

## 6.4 Discussion

The received waveforms appear to be similar in shape to those documented by Barkmann et al. [2000], suggesting that both sets of simulations were closely matched. Indeed, given that almost the same site was investigated and identical, or at least similar, material prop-
properties and simulation parameters were used, any major differences would be considered most unexpected.

From the Wave2000 simulations in this study, significant relationships can be seen between both the through velocity and the proportion of fast arriving energy, and cortical area. It is possibly expected that this is the case for the velocity measurements with the simulation. The thicker cortical walls would allow for the more direct crossing of the finger via the cortex. This more direct crossing through the bone, with a higher velocity than the surrounding soft tissue and marrow, may have explained the higher time of flight velocities observed for those with greater cortical area. This may even be accentuated by the partial volume effects, due to the resolution of the initial pQCT images [Anonymous, 2002]. Even where extremely small areas of soft tissue are incorrectly selected as cortical bone, due to their position within a voxel, they may allow for an unrealistic pathway across the phalanx.

It would be much more difficult to use this hypothesis in the real world because of the controversy over the effect of cortical thickness on the nature of the waves being propagated [Njeh et al., 1999b], and thus being received by transducers. It was therefore felt that while this approach provided promising results here, it was not appropriate for further investigation using the prototype.

The estimated Young’s modulus values based on the CT densities ranged from 12.7–22.1 GPa. These appear to be consistent with values found in the literature [Zysset et al., 1999], and confirm that the properties calculated for the bone were reasonable. However, with the exception of the fast and slow wave energy at 60% of the bone, the simple and complex models were closely matched. This suggests that the investigation using bone
with different properties for regions of different densities may be an unnecessary complication.

Perhaps the more interesting point to notice is the positive relationship that exists between the proportion of fast arriving energy and the cortical area. This seems to corroborate the results found by Cadossi and Cane [1996], who suggested that the profile of the early part of the wave was dependent on the thickness of the cortical bone. Using the above results, it seems possible that QUS could be used as a very simple, cheap means of determining bone condition. At the outset of this chapter, it was decided that cortical thinning, or cortical area, was the property of interest. Area is important as there is much evidence to suggest that reduced area is associated with an increased risk of osteoporosis. In work carried out recently looking at cortical area of metacarpals of healthy women and those with osteoporotic fracture, Crespo et al. [1998] showed that cortical area was significantly lower for the fracture sample. This was also the case for those with either Colles’ or vertebral fracture, suggesting that this type of measurement is ideal for determining the systemic risk of osteoporosis. The site used by Crespo et al. [1998], the metacarpal, is anatomically similar to the proximal phalanx and experiences similar loading patterns.

In other research investigating age-related changes in cortical bone, Iwamoto et al. [1998] studied metacarpal measurements of Japanese women from 42-94 years. In 229 volunteers, they noted no significant changes in bone width but a significant increase in marrow width from the 6th decade. This led to the significant decrease in cortical bone width, first detectable between 61-70 years, which equates to a reduction in cortical bone area. Similar effects were noted in this work, with a decrease from the fifth decade, however the small number of volunteers makes it impossible to determine significance. Another
interesting point to the work by Iwamoto et al. [1998] was the change in density. The correlation coefficient was greater for the change in cortical thickness than for cortical density with aging. Therefore, there is a greater expected annual decrease in thickness meaning that changes could be detected quicker than if density were used. In a comparative study that looked at similar changes in men, Iwamoto et al. [2000] found that reductions in thickness and density were less pronounced. This does not mean that thinning of the cortices does not occur for the males. Rather, males are protected by periosteal formation. This was documented by Duan et al. [2001], who found that bone formation on the periosteal surface resulted in a smaller net bone loss for men, when compared to women.

It therefore seems logical that the proximal phalanx may prove as useful as a site to investigate using QUS. Whilst velocity is not ideal for predicting material or morphological changes, energy measurements may prove useful. However, one major limitation of this work is the lack of evidence that cortical thinning at the proximal phalanx actually mirrors changes at the sites of interest from a densitometry point of view. Even though thinning of the cortex may be accepted as a manifestation of osteoporosis [Seeman, 2003b], predicting or monitoring changes are pointless if the results are not in line with the changes of BMD at the femoral neck or the lumbar spine. Therefore, it is proposed that before any large scale experimentation is undertaken, the relationship between cortical area at the phalanx and density at the femur or lumbar spine is investigated.

The trends observed for density as a function of age in the females in this study appear to mimic the expected profile. Although the sample was relatively small, there appeared to be an increase in density up to 45 years followed by a decrease after the approximate age at menopause. The small number of males (n=6) in the present study meant that no
worthwhile conclusions could be drawn about density changes with age.

The waveforms from repeat scans with varying frequency show that as frequency is increased, the output becomes more compact. This suggests that higher frequency scans would prove more problematic when it comes to defining and selecting the fast and slow waves. Indeed, visual inspection of the 2.0 and 5.0 MHz results from Figure 6.8 show that almost impossible to tell where this changeover occurs. The scans at 0.5 and 1.0 MHz remain as the best choice. By comparing the simulation at the exact time points when the bone wave, the medullary wave and the soft tissue wave arrive, the 1.0 MHz models gave the cleanest breaks. This was consistent for the simulations on all of the volunteers. This suggests that the initial choice of a 1.0 MHz signal was correct.

A second limitation with the above simulations is two dimensional nature of the input geometries. Although the cross section of the finger can be measured and plotted, the effects of the third dimension are ignored. The greatest expected effect of this simplification is that reflections and divergence into and out of the plane in question are missed. This was not seen as a major concern because the region of interest is the beginning of the received waveform. Both the time of flight velocity and the fast arriving energy are both computed from the earliest deviations from the zero amplitude.

The resolution of the pQCT scans was relatively crude, at 0.2 mm. Even if trabecularisation was occurring on the endosteal surface, this detail may not be captured. However, this level of resolution was deemed adequate for this initial hypothesis testing. The author acknowledges that further simulation, with more intricate geometries are necessary. It is suggested that this be done with cadaveric phalanges, which would allow exposure to higher levels of ionising radiation, resulting in much greater resolution. It may also help
reduce any errors caused by movement on the part of the volunteers.

6.5 Conclusions

It has been demonstrated that energy measurements may indeed be the key to predicting skeletal condition. If the area of the cortical bone can accurately determined, then the amount of thinning and progress of osteoporosis may be gauged. This theory however needs to be tested with more accurate CT scans and with the emphasis on comparison to the lumbar spine or femoral density.
Modelling and Simulation: Cadavers

*All exact science is dominated by the idea of approximation.*

Bertrand Russell

Previous simulations have shown that the basic morphology of the finger could be predicted by QUS. The following chapter attempts to address the limitations of the original study and expand the hypothesis to include a comparison with axial bone density. The goal was to reinforce the initial findings and determine their usefulness in a clinical setting.

### 7.1 Introduction

Chapter 6 investigated the possibility of predicting the morphology of the proximal phalanx with a view to monitoring changing bone quality. Although the results of this preliminary study were promising, there were a number of limitations that needed to be addressed before this link can be confirmed.

Of these, possibly the greatest drawback was the low resolution of the original CT
scans. For the preliminary study the resolution was deemed adequate, in so far as it gave an estimate of the shape and thickness of the bones of the finger at the exact region of interest. However, the precise detail of the cortical bone, especially as the endosteal surface was not properly recorded. This meant that the simulations may not be matched to real life measurements. Furthermore, partial volume effects may have led to inaccurate determination of cortical area and cortical thickness. This may have had significant consequences on the correlations found between the simulated QUS values and the morphology.

In addition to the issue of the resolution, there was no calculation of how well the thickness values matched the density of the axial skeleton. Whilst it may be fair to suggest the cortical thinning of the phalanx is a sign of bone loss, the fracture sites of interest are those at the hip and lumbar spine and it is density that these sites that is used to predict fracture. Therefore, before this method is accepted by clinicians there must be some study to determine the relationship between thickness of the phalanx and the density at these sites. In the past, the ultrasound parameters at the phalanx have been compared directly to DXA values (Chapter 2). The correlations have been shown to be significant, but this does not imply that this approach is best. Without comparing the structure of the finger and the femur or spine, the correlations could be assumed to be due to another unrelated systemic change.

In the previous simulations, the input geometries came from both men and women. Although there is bone lost on the inner surface for both sexes, the rate of loss and the formation of bone on the outer surfaces is different [Oyster, 1992]. To guarantee that the gender effects were not altering the waveform it is necessary to investigate a female only sample.
Finally, though results have proved positive to date, there has been no direct comparison between simulated values and measured values. The exact implementation of the simulation is not possible in real life, because it is assumed that all fingers are the same width. Therefore, no matter how well the simulations work, the approach would be pointless if the results could not be replicated in practice.

To address the issues raised, another, more accurate simulation study was proposed. The idea was to generate more detailed input geometries which could give more exact waveforms. Along with this, DXA values would be found to allow comparison with the density of the hip for the same individuals. Finally, the prototype device would be used to measure the finger at the same region of interest to determine if the results could be replicated in practice.

### 7.2 Methods

#### 7.2.1 Sample

The right femur and the entire second digit (including the distal section of the metacarpal) from the right hand were collected from 14 female cadavers (aged between 81 and 95 years) from the Academic Medical Center in Amsterdam. Ethical approval was granted by the university for all tests carried out on the specimens. All samples were stored in formalin.
7.2. Methods

7.2.2 µCT

The fingers were prepared for scanning by removing them from formalin and patting dry in a fume cupboard. They were then wrapped in tissue and placed in a specimen bag. The metacarpophalangeal and interphalangeal joints were marked to aid positioning in the sample holder and allow for investigation of the correct region of interest. The samples were placed in the sample holder of the vivaCT 40 machine (SCANCO Medical AG, Brüttsisellen, Switzerland). With the door locked, the software was prepared for the scan. Each sample was given a unique label which was based on the original hospital sample number. The same control file was used for all scans. This included all the parameters required to complete the scan. The resolution for the scan on each sample was 35 µm; resulting in voxels with edge length of 35 µm. A preliminary scan was carried out in order to find the area of interest on the phalanx. Using this scan, the phalanx length was measured and the region from 50% to ≥ 70% was selected for more extensive examination.

Evaluation of each section was performed using the in-built Bone Midshaft Evaluation function that is supplied with the vivaCT 40. This function evaluates the selected bone with the assumption that it approximates a ring of cortical bone. This was assumed to be appropriate for this work given that the bone is generally observed as an oval or D-shaped structure. Examples of this can be seen in Figure 7.1.

In order to perform the evaluation, the cortical bone must be properly defined. Contouring was performed along the outer and inner surfaces to accurately select the borders. The outer border was picked up by drawing a spline roughly approximating the periosteal surface in a counter-clockwise direction. The inner surface was picked up by drawing a spline approximating the endosteal surface in a clockwise direction. The original splines
7.2. Methods

(a) Cross section at 50%  (b) Cross section at 60%  (c) Cross section at 70%

Figure 7.1: The figures show slices of the proximal phalanx within the region of interest. The images are all taken from the same individual. The inner white structure is the cortical bone. This is surrounded by soft tissue which is seen here as the grey area. The outer white circle shows the inner diameter of the sample holder.

and the results of contouring can be seen in Figure 7.2. Unconnected trabeculae and trabeculae extending from the endocortical surface into the medullary cavity were not included. Contouring using these two splines resulted in the correct choice of bone for each slice. The areas created were manually inspected to ensure no bone was excluded and no soft tissue was erroneously included. The evaluation process uses these approximations of the shape of the cortical bone and the knowledge that slices are 35 µm apart to create the volume to test.

The results of the evaluation are presented in an output file along with a reconstruction of the section investigated. An example of an output file can be seen in Figure 7.3. The calculated bone and tissue density are both presented. Tissue density is the density value based on the density of the bone and included pores. The results of direct and plate analysis are also printed to the file. Only the thickness values from the plate method analysis are used. Area is assumed to be cortical thickness times the curve equidistant from the inner and outer surface (Centre Curve). Volume is calculated using the area times the length of the scan in the axis of scanning (Length). Rearranging these we get Equation 7.1.
Figure 7.2: The software used by the vivaCT 40 machine. Sample splines (green lines) drawn close to the perioseal and endosteal surface can be seen (a) along with the curves generated as a result of automatic contouring (b).
7.2. Methods

\[ \text{Bone Volume} = \text{Cortical Thickness} \times \text{Centre Curve} \times \text{Length} \quad (7.1) \]

The bone surface is calculated by multiplying the inner and outer circumference by Length. Therefore, the Centre Curve multiplied by Length is equal to half the bone surface. Using this information, Equation 7.1 can be written in terms of Cortical Thickness, Bone Volume and Bone Surface, as per Equation 7.2.

\[ \text{Cortical Thickness} = \frac{\text{Bone Volume} \times 2}{\text{Bone Surface}} \quad (7.2) \]

The direct method thickness would be greatly affected by pores. For example, imagine both techniques used on the same sample of bone. Then a small pore was added to the centre of the cortex. The bone surface would change by a small amount, thus the plate model thickness would not be altered greatly. However, the direct model thickness would be halved because there is now a pore between the inner and outer surface.

The cortical thickness, cortical area, bone density, tissue density and the porosity were recorded for each phalanx. These were then used for comparison with one another, with simulated QUS parameters, prototype QUS parameters and with DXA data from the femur of the same individuals.

7.2.3 Simulation

The simulations were carried out using Wave2000 (CyberLogic Inc, New York, NY, US). The input geometries used for simulation were taken from ISQ file. This is a file which contains all the slices images stacked in the sequence they were scanned. This was decon-
Figure 7.3: Sample results file for *Mid Shaft Evaluation*. Both bone and tissue density are presented along with the results of direct model and plate model analysis.

structured into the original slice images, in TIF format, and those of interest were used for further analysis.
Image Processing

In order to use the images from the µCT scans some preparation was required. This included rotating the finger to the expected orientation, thresholding the image so that soft tissue was removed and cropping the image to the area of interest. Images were rotated based on visual examination such that medial and lateral sides were on aligned left and right, and the dorsal and ventral surfaces were aligned top and bottom. Thresholding was then performed, using ImageJ. The lower and upper limits were set to zero and 100 respectively. This resulted in an image where each pixel is set to one or zero based on its’ grayscale value. One represents cortical bone and is filled white, and zero is soft tissue and is filled black. Finally, the area containing the ring of cortical bone was cropped to a square area 16 mm × 16 mm.

The images created above were used as the input geometries for the simulations. The resolution was set to 28.571 pixels/mm. This is equivalent to the scanning resolution of the µCT; 35 µm. All other model parameters were set to recreate those of the prototype. The transmitter and receiver were modelled as straight lines on the left and right hand sides of the geometry. The input was a signal with a frequency of 1 MHz run for 1 µsec. Snapshots of a sample simulation can be viewed in Figure 7.4.

Measuring Simulated QUS Parameters

The energy of the fast and slow wave were calculated. In order to separate these into their component parts, the wave through a sample without bone was simulated. The resultant waveform can be seen in Figure 7.5. The start and end of the wave that crosses the geometry where noted and used to determine the start and finish of the slow wave.
7.2. Methods

(a) 1 µs  
(b) 3 µs  
(c) 5 µs  
(d) 7 µs  
(e) 9 µs  
(f) 11 µs

Figure 7.4: The passage of ultrasound through the finger can be seen in these images. The pulse originates from the transmitter on the left hand side (a) and is detected by the receiver on the right hand side. Figures (b) and (c) show the waves travelling faster through the cortical bone and medullary canal. In figure (d) the cortical wave approaches the receiver. This is followed by the wave that has travelled through the medullary cavity (e) and the soft tissue (f).

The slow wave energy was the integral of this section of the rectified waveform. The fast wave energy was the integral of the rectified wave up to the start of the slow wave.

7.2.4 QUS

The prototype scanner was connected to the controlling computer and setup to allow for scanning each finger as would be for live volunteers (see Figure 7.6). Each finger was removed from the formalin and patted dry with tissue. The proximal phalanges were measured on the dorsal side with both the metacarpophalangeal and interphalangeal joints
7.2. Methods

(a) Waveform through Geometry

(b) Waveform through Sample Phalanx

**Figure 7.5:** The wave through the geometry with no bone present, Figure (a), was used to determine the start and finish points (the dashed grey lines) of the wave travelling through the soft tissue. These were then used to determine the fast and slow waves, Figure (b), of the rectified wave of samples with bone present.
flexed. Using a permanent marker 50, 60 and 70% length of the phalanx were marked (see Figure 7.6). The finger was then placed in the prototype scanner, with the first marker (50% length) in line with the centre of the silicone pads, and aligned as it would be in ‘normal’ use, i.e. the long axis parallel with the table surface. The finger was then allowed to rest for 30 seconds to allow the soft tissue to stabilise, tissue fluid to relocate and any unusual settlings to disappear. Three repeat measurements were then taken with repositioning between scans. This was then repeated for each marked sites.

![Setup of prototype](image1)

![Finger with markings](image2)

**Figure 7.6:** Setup of the prototype scanner and finger for QUS scanning. The finger is marked at the regions of interest as detailed previously and then placed between the transmitter and receiver.

The energy arising from different paths was then computed. The computation involves determining the trigger point, the time of the first amplitude above a threshold, and the time of the maximum amplitude. An example of a received waveform can be seen in Figure
7.2. Methods

7.7 with both the trigger point and maximum amplitude marked. The maximum amplitude was found, along with the times where the slope of the wave changes sign before and after this point. This part of the wave, the slow wave, is then integrated, giving the slow wave energy. The wave from the trigger point to the beginning of the slow wave, the fast wave, was also selected and integrated. This gave the fast wave energy. The proportion of the fast wave energy to fast and slow wave energy was then calculated.

Figure 7.7: The area under the peak of the maximum amplitude, filled with the dotted pattern, is called the slow wave energy. The area under the wave from the trigger point to this area, filled with the zig-zag pattern, is call the fast wave energy.

Plotted Against
7.3 Results

7.3.1 µCT

There was a significant, negative correlation between the intra-cortical porosity and the average cortical thickness of the region evaluated. The correlation coefficient based on this sample was $R = 0.943$ ($P < 0.001$). This relationship can be seen in Figure 7.8.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Porosity_Cortical_Thickness.png}
\caption{Intra-cortical porosity plotted against the cortical thickness. The cortical thickness is an average value for the entire region evaluated.}
\end{figure}

There was a significant positive correlation between both the tissue density and the bone density with average cortical thickness. The correlation was greater for the tissue density. The coefficients of correlations were $R = 0.963$ and $R = 0.753$ ($P < 0.001$ and $P < 0.05$ respectively). These are both plotted in Figure 7.9.

Porosity displayed negative relationships with tissue density and bone density. The correlation coefficient was greater for the relationship with tissue density, $R = 0.994$ ($P < 0.001$), than for bone density, $R = 0.817$ ($P < 0.01$).
Figure 7.9: Tissue Density (a) and Bone Density (b) plotted against the average cortical thickness for the region investigated.

Tissue density and bone density were related $R = 0.868$ ($P < 0.005$), as can be seen in Figure 7.11.
7.3. Results

(a) Porosity Plotted Against Tissue Density

(b) Porosity Plotted Against Bone Density

Figure 7.10: Intra-cortical porosity plotted against tissue density (a) and bone density (b).

7.3.2 Simulated QUS

There were significant, positive correlations between the simulated PRO values and the cortical areas at all sites. These can be seen in Figure 7.12. The correlation coefficients were \( R = 0.6976 \ P < 0.05 \), \( R = 0.6775 \ P < 0.05 \) and \( R = 0.8231 \ P < 0.05 \).
7.3. Results

Figure 7.11: Tissue Density is plotted against Bone Density.

7.3.3 QUS

The significance of the correlations between the PRO from the prototype and the measured cortical thickness was varied. For 50% \( R = 0.6739 \) (\( P < 0.05 \)), for 60% \( R < 0.05 \) (\( P = < 0.05 \)) and for 70% \( R = 0.7250 \) (\( P < 0.05 \)). The precision for PRO measurements was 5.4%.

7.3.4 Cortical Thickness Plotted Against DXA

There was a positive relationship between the cortical thickness at the proximal phalanx and the density as measured using DXA at the neck of femur (Figure 7.14). The correlation coefficient was \( R = 0.918 \) (\( P < 0.001 \)).
7.3. Results

![Graphs showing PRO at different percentages (50%, 60%, 70%) plotted against cortical thickness.](image)

(a) PRO at 50%
(b) PRO at 60%
(c) PRO at 70%

**Figure 7.12**: PRO as calculated using the waveforms collected from the simulations plotted against the cortical thickness.
7.3. Results

(a) PRO at 50%

(b) PRO at 60%

(c) PRO at 70%

Figure 7.13: PRO as calculated using the waveforms collected using the prototype plotted against the cortical thickness.
7.4 Discussion

The observed increase in porosity as cortical thickness is reduced is expected and agrees with common beliefs [Seeman, 2003a]. It supports the theory that resorption of bone, especially on the endocortical surface, causes trabecularisation which leads to expansion of the medullary canal. This phenomenon has been observed at many skeletal sites [Duan et al., 2001], and up to this point was assumed to be occurring at the proximal phalanges. It has been shown that these assumptions were indeed correct and that thickness may prove useful as a measure of bone integrity.

The fact that both tissue and bone density showed a positive correlation with cortical thickness is important. This tells us that all the material and morphological properties of the bone are changing. One of the goals of this chapter was to show that one could accurately predict cortical thickness with the use of a quantitative ultrasound. It is reassuring to know that as the cortical bone is thinning the other expected changes, such as a decrease in density, are also occurring.

Figure 7.14: Comparison of cortical thickness of the proximal phalanx and density at the neck of femur in the same individuals.
The greater correlation of the tissue density with cortical thickness is due to the effect of porosity. As tissue density is greatly affected by pores, the increased porosity results in lower density. The fact that the bone density also appeared to be correlated with the cortical thickness may be more surprising. What has been observed here suggests that both the amount of bone and the density of the remaining bone alter.

The strong correlation found between the tissue density and the porosity can be explained by the fact that the increase in porosity results in pores in the bone which reduce the measured tissue density. The correlation, although slightly weaker, between the porosity and bone density is more difficult to explain. One possible explanation is that the imbalance between the bone resorption and deposition leaves a large number of resorption cavities.

All in all, the µCT analysis suggests that these measurements are cross correlated. Therefore, by being able to determine one, for example by the use of quantitative ultrasound, one can be confident that the others are also changing at the proximal phalanx.

There were strong correlations between the PRO from the simulations and the cortical thickness of the phalanges. The correlations were as strong as those found in the preliminary simulation study (Chapter 6). It is important to realise that this study was compared to the cortical thickness, not the cortical area. It was deemed acceptable to use cortical thickness here, as the resolution allowed for accurate measurements. This confirmation of the dependency of the energy measurements on the structure of the finger supports the original hypothesis that QUS at the finger could be used to predict changes in skeletal condition.

The PRO measured using the prototype showed significant positive correlations with
the measured cortical thicknesses at all sites, however these correlations were slightly less than for the simulated values. The values may be expected to be less than those of the simulations, as there are certain issues associated with measuring the fingers in the real world. For example, within the simulation software it is possible to align the finger so that the transducers are perfectly aligned on the left and right of the finger. In practice, of course, it is impossible to align the transducers perfectly on either side of the bone. Similarly, there is a potential to measure the incorrect region of interest due to the fact that the soft tissue is marked and then measurements are made. The soft tissue does move during the positioning of the transducers, and therefore the marking may not remain of the desire area of the phalanx. Whilst every effort is made to ensure the finger is positioned accurately, some error is expected. The error due to alignment issues is not excessive, as demonstrated by the coefficient of variation of 5.4% for the PRO.

Again, as with the previous simulation, there is also the limitation that the simulation only works in two dimensions. The prototype measures a three dimensional profile, and some noise in the received waveform may be due to dispersion or reflections along the bone. These were however considered negligible as the results from the prototype were in the same range as the simulated values.

The other major difference is the techniques used to calculate PRO. Because the simulations place the fingers in geometries of the same size, time thresholds can be used to separate the energy from different pathways. However, because in real life the fingers are different sizes the same technique cannot be used by the prototype. The idea of using the largest peak as the pick up point of the slow wave was used to combat this. Although this allows the calculation of ‘an’ estimation of the fast and slow energy, it is slightly dif-
7.5 Conclusions

QUS may be used to predict cortical thickness. This may prove to be an extremely useful tool given that cortical area decreases with osteoporosis. The fact that the prototype matched the results from the *in vivo* work and the results of the simulation here allow us to believe that this methodology has some future.
Conclusions and Future Work

*I seldom end up where I wanted to go, but almost always end up where I need to be.*

Douglas Adams

8.1 Conclusions

One of the goals set out at the beginning of the research project was to identify the most significant risk factors for osteoporosis for a British population. This were achieved in a manner of speaking, but a number of other questions have been raised along the way.

A simple questionnaire based risk index was developed. By measuring age and weight and asking if an individual has suffered a non traumatic fracture or taken hormone replacement therapy, a clinician may better decide on the best course of action. These tools performed quite well in both the development and validation stages. They had high sensitivities and high specificities, meaning that those with the highest and lowest risk of osteoporosis could be dealt with in the best possible manner. Indeed, the very high specificities at the femoral neck and total hip in particular meant that a large percentage of the
unnecessary scans that clog the health service at the moment could be prevented.

The addition of QUS at the calcaneus seemed to increase the utility of these tools in the development stages, by removing even more healthy people. However, the validation of these suffered due to the fact that the threshold that was selected previously did not allow for the correct selection of those at greatest risk. This does not mean that there is no place for a system that combines these two techniques, but a method that does not suffer if one systems fails would be safer. For example, using the simple assessment tool and QUS separately and then assigning osteoporosis, or rather risk of osteoporosis, if either technique suggests so may prove more effective.

Traditional QUS measurements at the finger proved unsuccessful at predicting density at the hip or spine. This is most probably due to the discordance already discussed [Faulkner et al., 1999]. There may be decreases in measured QUS parameters at all sites of interest, however the rate of change does not always match the change in density at other sites. The fact that QUS was not able to discriminate between those with high or low density at either the lumbar spine and hip for a postmenopausal sample is concerning. One might argue that by including young, healthy individuals the results become more appealing. However, is it correct to include these? The author feels that it is not, as the young and healthy can be assumed to be free from the risk of osteoporosis, with the exception of those who present with secondary causes. Therefore, if the changes in QUS do not reflect changes in DXA for an entirely postmenopausal population they will have little practicality as screening tools.

The disappointing correlations between the DXA and QUS prompted the testing of the proportion of fast to slow wave energy (PRO) at the proximal phalanx. The initial
results seemed very promising, with a very strong correlation between PRO and cortical area along the diaphysis of the phalanx. Cortical area was used in this case as a surrogate for cortical thickness, as partial volume effects would have influenced thickness values to a greater extent. The relationship between these values did not take into account the exact processes that were taking place on the endosteal surface, but were assumed to be representative.

The second set of simulations carried out using cadaveric specimens supported the claims that energy measurements could be used to monitor cortical thinning. PRO was strongly correlated to the thickness as computed by the μCT machine. μCT also allowed the representation of pores and the trabecularisation, which appeared not to affect the results.

It seems that in terms of clinical densitometry we have gone full circle to a time where the principles of radiogrammetry are once again in fashion. However, this time the cortical thickness can be found very quickly and cheaply using QUS. One of the major limitations of radiogrammetry - the ignoring of what is happening in the bone - also seems to be dealt with. From the second set of simulations it appears that the energy measurements used to predict the thickness hold true even with the presence of large pores on the endocortical surface.

Furthermore, this time around, the cortical thickness is not the definitive measurement, it is simply an indication that overall skeletal quality is altered. DXA T-scores remain the gold standard for diagnosing osteoporosis and for this reason the results were compared to the density at the femoral neck. The excellent correlation between the cortical thickness of the phalanx and the density at the femur suggest that the use of such measurements is
appropriate. This is much more than can be said for the QUS parameters tested in Chapter 5, where there was almost no agreement with axial density.

There is also some evidence in the literature that changes in cortical thickness at sites similar to the those observed in the proximal phalanx are significantly different in those who have suffered a fragility fracture [Crespo et al., 1998]. The link between thickness and the risk of fracture has been alluded to here, via the common association with low DXA T-scores. Of even greater importance, these values were seen to be significantly different in postmenopausal women. During the course of the work done in the Great Western Hospital in Swindon, it was shown that the current QUS measurements struggle to categorise people based on risk because of the error in the measurements. This ability to select those with fracture and the large differences between healthy and osteoporotic subjects provides further evidence that energy measurements may be the way forward when it comes to prescreening for DXA.

8.2 Future Work

There are many questions yet to be answered with regard to QUS in postmenopausal women. Whilst the assessment tools that used QUS in the development study performed exceptionally well, the results were not repeated in the validation study. The author suggests that in the future, risk assessment tools and QUS are used together, but instead of combining the outputs, it may be better to deal with them in a parallel fashion. This way, the operator can get an idea of how well a patient performs in each, instead of relying on a single result.
The development of energy measurements to predict structure at the finger may be the most fruitful deliverable. Although the sample was small in both the simulations and in the prototype testing of this technique, the results were impressive. It is accepted that a much larger study is needed to confirm these results. It is also suggested that any such analysis continue looking at only postmenopausal women, as including completely healthy subjects may give over optimistic predictions.

Furthermore, there is definite scope to develop this method to predict those most likely to suffer a fracture. As was mentioned previously, cortical thickness at the metacarpal was significantly reduced for those with an osteoporotic fracture. This remained true when investigating only postmenopausal individuals. Therefore, if accurate predictions of thickness (or thinning) are possible, the potential for warning those at greatest risk is immense.
Bibliography


R. Barkmann, S. Lusse, B. Stampa, S. Sakata, M. Heller, and C. C. Gluer. Assessment of the


S. Boonen, J. Nijs, H. Borghs, H. Peeters, D. Vanderschueren, and F. P. Luyten. Identifying postmenopausal women with osteoporosis by calcaneal ultrasound, metacarpal digi-


L. K. H. Koh, W. Ben Sedrine, T. P. Torralba, A. Kung, S. Fujiwara, S. P. Chan, Q. R. Huang,


G. Liu, M. Peacock, O. Eilam, G. Dorulla, E. Braunstein, and C. C. Johnston. Effect of


E. Minnock, R. Cook, D. Collins, J. Tucker, and P. Zioupos. Using risk factors and quanti-
tative ultrasound to identify postmenopausal caucasian women at risk of osteoporosis.


Volunteer Questionnaire
LIFESTYLE/QUESTIONNAIRE INTERVIEW

Patient Number      Weight……………………..
Date of Birth…………………..   Height……………………..
Age……………………………

Q1 Which of the following best describes your daily work or other daytime activity that you usually do?

☐ 1 I am usually sitting and do not walk about much
☐ 2 I stand or walk about quite a lot, but do not have to carry or lift things very often
☐ 3 I usually lift or carry light loads or have to climb stairs or hills often
☐ 4 I do heavy manual work or carry heavy loads often

Q2 On average, how often do you engage in vigorous physical activity in leisure time?
   (activity that makes you breathless and sweat e.g. jogging, aerobics, football, tennis, squash, competitive sports etc)

☐ 1 Rarely / infrequently
☐ 2 Once / twice a month
☐ 3 Once / twice a week
☐ 4 Daily

Q3 How do you rate your present physical fitness for your age?

☐ 1 Below average
☐ 2 Average
☐ 3 Good
☐ 4 Very good
**Q4** In the following age groups did you take exercise for 20 mins or more a day?  
(tick as appropriate)  
- [ ] 1 under 20yr  
- [ ] 2 between 20 and 35yr  
- [ ] 3 between 35-55yr  
- [ ] 4 over 55 yrs

**Q5** How often and how much do you smoke?  
- [ ] 1 I smoke every day  
  
  (number of cgrts/day) ________
- [ ] 2 I smoke occasionally, but not every day
- [ ] 3 I used to smoke, but do not smoke at all now  
  (fill in next question as well)
- [ ] 4 I have never smoked

**Q6** In the following age groups how much did you smoke?  
(number of cgrts/day)  
- [ ] 1 under 20yr  
- [ ] 2 between 20 and 35yr  
- [ ] 3 between 35-55yr  
- [ ] 4 over 55 yrs

**Q7** How often and how much alcohol do you consume?  
(Estimate of the number of units per week e.g. a unit is ½ pint of beer, 1 glass of wine or 1 measure of a spirit)  
(estimate of units/week)  
- [ ] 1 I drink alcohol every day of the week  
  
  __________
- [ ] 2 I drink alcohol about 3 or more days a week  
  
  __________
- [ ] 3 I drink alcohol about once or twice a week  
  
  __________
- [ ] 4 I do not drink alcohol  
  
  __________
Q8  In the following age groups how much alcohol did you consume?  
(Estimate of the number of units per week e.g. a unit is ½ pint of beer, 1 glass of wine or 1 measure of a spirit)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Estimate of Units/Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>under 20yr</td>
<td>___________</td>
</tr>
<tr>
<td>between 20 and 35yr</td>
<td>___________</td>
</tr>
<tr>
<td>between 35-55yr</td>
<td>___________</td>
</tr>
<tr>
<td>over 55 yrs</td>
<td>___________</td>
</tr>
</tbody>
</table>

Q9  Have you had any previous broken bones?  

Yes/No  ______

If yes, which bone did you break? (Please state whether left or right if extremity)

Q10 When and how did the break occur?

Q11 Have any members of your family suffered from broken bones as a result of osteoporosis?  

Yes/No  ______

Fracture site………………………………………………………………………………………………

Q12 Have any members of your family suffered from osteoporosis?  

Yes/No  ______

Relationship to interviewee………………………………………………………………………………

Q13 Have you ever been confined to your bed for more than two months?  

Yes/No  ______

If so, why and for how long?………………………………………………………………………………
Q14 Have you ever had any other health problems?
   Yes/No       ______
   Details........................................................................

Q15 Have you ever taken Steroids?
   Yes/No       At what age.................................
   For how long?...........................................

FOOD STUDY

Q16 Have you ever seriously controlled your weight?
   Yes/No       At what age.........................
   For how long?.................................

Q17 Do you take calcium supplements?
   Yes/No       ______
   For how long?...........................................

Q18 Do you have any specific dietary restrictions/requirements?
   Yes/No       ______
   Details...................................................................

Q19 Do you eat the following foods – milk, cheese, yoghurt, fish, eggs and nuts?
   (Please tick as appropriate.)
   □ 1 never
   □ 2 once a week
   □ 3 2-4 times a week
   □ 4 daily

A9
Q20  Do you eat the following foods daily?  *(tick as appropriate)*

Vegetables
Fruit
Bread, cereals, rice and pasta
Milk, yoghurt and cheese
Meat, poultry and nuts

Q21  Have you ever had any problems with your diet during your life?  
If so, at what age?  *(details)*

- under 20yr
- between 20 and 35yr
- between 35-55yr
- over 55 yrs

Q22  How do you rate your diet compared with your peers?

- Below average
- Average
- Good
- Very good
Q23  Do you have any children?
Yes/No  How many?……………..

Q24  Did you breast-feed your children?
Yes/No  For how long?……………..

Q25  At what age did your periods start?
……………………….years old

Q26  At what age did your periods stop?
……………………… years old

Q27  Have you had a hysterectomy?
Yes/No  How long ago?………..
at an Age of ………………

Q28  Have you had your ovaries removed?
Yes/No  How long ago?………..
at an Age of ………………

Q29  Have you ever taken the oral contraceptive pill?
Yes/No  How long ago? ........
For how long? ........
at an Age of ………………

Q30  Have you ever used/Are you still using HRT?
Yes/No  How long ago? ........
For how long? ........
at an Age of ………………
Appendix B

Risk Factor and QUS Article
Using Risk Factors and Quantitative Ultrasound to Identify Postmenopausal Caucasian Women at Risk of Osteoporosis

Enda Minnock, Richard Cook, David Collins, Julie Tucker, and Peter Zioupos*

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Abstract

There is a need to prescreen large numbers of individuals for osteoporosis due to current demands on clinical resources. Some previous attempts to predict individuals at risk have used simple indices based on patient information, or Quantitative Ultrasound (QUS) and have shown good sensitivity but also demonstrated low specificity, which means that many individuals with good bone mineral density were also selected. The aim of this study was to determine if a tool based on a combination of risk factors and QUS measurements could also be made to provide improved specificity. A risk factors measurement questionnaire was created and completed for a sample of Caucasian postmenopausal women (n = 235) who had undergone Dual-energy X-ray Absorptiometry scanning. QUS measurements were also taken at various skeletal sites. Assessment tools were generated using stepwise regression to predict osteoporosis, evaluated by receiver operating characteristic curves, and assessed using area under the curve values. Specificity values were determined at a sensitivity of 0.90 to establish the comparative utility of each assessment tool. Using only a risk factors model the specificities were 0.28 at the lumbar spine, 0.45 for the femoral neck and 0.68 for the total hip. In a risk factors + QUS data model the specificities measured were 0.44 for the lumbar spine, 0.78 for the femoral neck, and 0.84 for the total hip. These novel assessment tools can identify those with low bone mineral density at a number of skeletal sites and help towards avoiding many unnecessary investigations in the future.

Key Words: Bone mineral density; osteoporosis; quantitative ultrasound; questionnaires; risk factors.

Introduction

The skeletal condition osteoporosis is characterized in cancellous bone by a reduction in the apparent density and structural integrity of the bone and thinning of the trabeculae within the 3D network. These effects result in the reduced mechanical integrity of the tissue and the low trauma fractures, which are characteristic of the condition. The selection of individuals with low Bone Mineral Density (BMD) is important as it enables the early application of treatments that can lower the risk of fracture. The determination of BMD by Dual-Energy X-ray Absorptiometry (DXA) is widely accepted as the standard method for the assessment of axial skeletal density and it is the T-scores determined on the basis of a BMD measurement on which the World Health Organization and the International Society for Clinical Densitometry base the definition of Osteoporosis. The problem arises, that the densitometry equipment is expensive and requires a skilled radiographer if high-quality results are to be obtained. As a result, densitometry services are frequently hospital based, expensive to run and, due to the increasing number of people at risk and age of the population, running beyond capacity. Indeed, a report carried out by the National Osteoporosis Society suggested that an additional 126 axial DXA scanners are required to cope with the current and future needs of the National Health Service (NHS) (1).
The potential to have a method of screening large groups of individuals so that selection and prioritization can occur is an attractive proposition. This will enable earlier detection and diagnosis of those individuals most at risk of osteoporosis. Many groups have attempted to produce simple assessment tools based on easily attainable patient information (2–7). These tools were generated to predict those at the highest risk of osteoporosis for immediate priority treatment and those at low risk could perhaps be reassessed at a later date. The use of Quantitative Ultrasound (QUS) has been shown to have a moderate-to-good ability to predict osteoporosis in postmenopausal women, depending on the technique and the site of investigation (8–11).

The idea of combining risk factors and QUS measurements to predict osteoporosis has been less extensively explored. The study by Richy et al. (12) demonstrated that a combined tool using both QUS at the proximal phalanx and a risk factor based assessment, could improve the diagnostic ability over and above that which was obtainable by the use of the individual methods separately. Pongchayakul et al. (13) compared how a score based on age and weight, QUS at the calcaneus and a combination of both these techniques for predicting osteoporosis at the femoral neck. They found that for a Thai population the combination model had a significantly higher Area Under the Curve (AUC).

The down side of these screening methods is that they focus primarily on the correct selection of those most at risk of osteoporosis. This has led to promising predictive abilities, but at the expense of specificity, which is the ability to correctly select those individuals not at risk of osteoporosis. As a result the numbers of individuals being selected as needing a densitometry investigation when it is not a priority remains high.

The aim of this study was to analyze risk factors associated with osteoporosis and a variety of QUS measurements, at various skeletal sites, to determine if a combination of these could be used to discriminate between patients with osteoporosis and those with BMD within the normal range, maintaining high levels of sensitivity but also achieving good specificity.

Methods

Sample

The initial sample comprised 274 postmenopausal (natural and surgical) Caucasian women who were referred to the DXA scanning clinic at Great Western Hospital, Swindon, UK. Referral was performed by the patients GPs, or hospital based clinics. Informed written consent was obtained from all patients prior to inclusion into the study. Presence of a disease or condition that is known to cause secondary osteoporosis was seen as an exclusion criterion (2 patients had hyperthyroidism, 1 had Cushing’s, and 5 celiac disease).

Questionnaire Design and Execution

Our questionnaire was created as an extension of a number of ad hoc questionnaires that are currently in explorative use in various UK NHS hospitals. We called it Risk Factors Measurement questionnaire and it was extended to 30 questions with emphasis on physical activity, smoking and alcohol habits, medical history, diet, and reproductive history (Electronic Supplementary Material Appendix). One skilled researcher (RBC) completed the responses consistently for all patients. The use of hormone replacement therapy (HRT) was determined if duration of use was ≥1 yr and treatment began before the age of 60 yrs. Patient height and weight were also recorded as part of the questionnaire. Eight patients were excluded due to a lack of information regarding any previous medical problems. Twenty-three questionnaires were found to be missing necessary information and were subsequently excluded from the sample. A sample of 235 patients was finally chosen upon which analyses could be carried out. The demographics of the sample studied can be seen in Table 1.

Dual-Energy X-ray Absorptiometry

All DXA scanning was carried out by a qualified radiographer using a Hologic QDR-4500C (Hologic Inc., Bedford, Mass.). BMD values were determined for the lumbar spine, femoral neck, and total hip and the corresponding T-score (BMD T-score) values were calculated based on the National Health and Nutrition Examination (NHANES) database.

Quantitative Ultrasound

QUS measurements were taken using the CUBA Clinical (McCue plc, Winchester, UK) system and Sunlight Omnisense (Sunlight Medical, Rehovot, Israel) system. Aquasonic Clear Ultrasound Gel (Parker Laboratories Inc, Fairfield, NJ 07004) was used to ensure coupling between scanner and site of measurement. Quality verification was performed on each day of testing on both machines using phantom blocks. All measurements were carried out by the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean (± SD) or number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>59.7 (± 10.8)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.6 (± 12.4)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.0 (± 7.2)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.4 (± 4.6)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>32 (13.6%)</td>
</tr>
<tr>
<td>Age at menarche (yrs)</td>
<td>13.0 (± 1.9)</td>
</tr>
<tr>
<td>Age at menopause (yrs)</td>
<td>44.8 (± 8.0)</td>
</tr>
<tr>
<td>NTB (history of non-traumatic fracture)¹</td>
<td>76 (32.3%)</td>
</tr>
<tr>
<td>HRT (use of hormone replacement therapy)²</td>
<td>109 (46.4%)</td>
</tr>
<tr>
<td>BMD T-score ≤ −2.5 at any site</td>
<td>56 (23.8%)</td>
</tr>
</tbody>
</table>

Abbr: SD, standard deviation; NTB, nontraumatic fracture; HRT, hormone replacement therapy; BMD, bone mineral density.

¹NTF was defined as a fracture resulting from minimal trauma based on the Risk Factors Measurement questionnaire responses.

²HRT was assigned if use was ≥1 yr and treatment began before the age of 60.
same trained operator who was familiar with both systems. The CUBA Clinical system measures the Broadband Ultrasound Attenuation (BUA, db/MHz) and the Velocity of Sound across the calcaneus (VOSCAL, m/s). The Sunlight Omnimesh was used to measure the axial Speed of Sound (SOS) at 3 sites; the distal radius (SOSDR), the proximal phalanx of the middle finger (SOSPP), and the midshaft tibia (SOSMT). It was not always possible to obtain a reading for all sites utilizing the Sunlight Omnimesh. In the few cases where site measurements were not obtainable analyses were carried out on the available subsample.

The precision for each QUS measurement was calculated based on repeated measurements for 50 volunteers (34–80 yrs). Repositioning took place between measurements. The RMSECV were calculated as 3.06% for BUA at the calcaneus, 0.27% for Velocity of Sound at the calcaneus, 0.67% for SOS at the distal radius, 1.07% for SOS at the proximal phalanx, and 0.67% for the mid tibia.

**Statistical Analyses**

Regression analysis was performed between all questionnaire responses and the T-scores at the 3 chosen BMD measurement sites. Variables for which correlations gave \( p < 0.2 \) were entered in multivariate analyses. This consisted forward and backward stepwise regressions using the above selected variables as the independent variables and the T-scores as dependent variables. Variables were only retained if they were significant at \( p < 0.05 \). This was then repeated with the inclusion of each QUS measurement as independent variables. This generated multivariate equations with both risk factors and a single QUS measurement used to predict BMD T-score at each of the 3 sites. Regression analysis was also carried out between QUS measurements and the BMD T-scores to determine the diagnostic ability of each QUS measurement independently and for comparison with the assessment tools developed using risk factors.

**Receiver Operating Characteristic Curve Analysis**

The sensitivity and specificity values were calculated for each of the multivariate regression equations and were used to create Receiver Operating Characteristic (ROC) curves. AUC analysis was carried out on each regression equation to determine diagnostic ability. These AUC values were used to determine the best performing assessment tools derived from risk factors and from a combination of risk factors and a QUS measurement. Specificity values and cutoff points were calculated for these assessment tools (all for a sensitivity \( \geq 0.90 \)). The Positive Predictive Value (PPV) and Negative Predictive Value (NPV) are also presented at these cutoff values.

**Simplification of Multivariate Regression Equations**

The best performing assessment tools (judged on their AUC values) were then simplified to create operator-friendly (not requiring a PC or other analytical tools) assessment tools. The coefficients of the multivariate regression equation were scaled and rounded so that they became integers. The result of this process was the production of a number of simplified, uncomplicated and operator friendly formulae. The AUC values of these new simplified assessment tools were calculated to determine if diagnostic ability had been compromised as a result of the simplification process.

**Software**

Statistical analyses were carried out using Minitab™ Statistical Software Release 13.31. ROC Curves and AUC values were produced using SigmaPlot ® for Windows ® Version 10.0.

**Results**

**Regression Analysis**

Regression analysis for each of the 3 sites (lumbar spine, femoral neck, total hip) identified 3 lists of suitable risk factors (based on the Risk Factors Measurement questionnaire responses), which were significantly correlated (at a moderate level of \( p < 0.2 \)) with the T-scores. From the QUS measurements BUA \((r = 0.57-0.65)\), VOSCAL \((r = 0.50-0.55)\), SOSDR \((r = 0.30-0.35)\), and SOSPP \((r = 0.33-0.39)\) were all positively correlated to the BMD T-score at each of the 3 sites \((p < 0.001)\). Meanwhile, SOSMT was weakly positively correlated \((r = 0.22)\) to the BMD T-score at the lumbar spine \((p < 0.005)\); but did not correlate to BMD T-score for the femoral neck, or total hip.

**Multivariate Equations—Risk Factors**

Stepwise regression determined the significant risk factors for predicting osteoporosis at each DXA site. As an outcome patient “age,” “weight,” “history of nontraumatic fracture” (NTF) and use of HRT were in all cases part of the those significant equations for predicting osteoporosis at all 3 BMD-assessed sites.

**Multivariate Equations—Risk Factors and QUS Data**

When BUA was added to the significant risk factors as an extra predictor variable for osteoporosis it was found to be significant \((p < 0.05)\) and was present in all regression equations. At the lumbar spine the independent variables identified by the analysis were BUA, weight, NTF, and HRT. For the femoral neck and total hip the variables were similar to those above, with “age” becoming significant and HRT dropping out.

When VOSCAL was considered along with the significant risk factors, it was found to be a significant variable for predicting osteoporosis at all 3 sites. For the lumbar spine, the variables chosen were VOSCAL, weight, height, NTF, and HRT. For the femoral neck and total hip, the same variables were identified except that “height” and HRT became insignificant.
When SOSDR and SOSMT were used in conjunction with the significant risk factors, they featured only in the linear models used to predict osteoporosis at the lumbar spine. SOSDR was used with weight, NTF and HRT, whereas SOSMT used these same variables plus age.

When SOSPP was used with the significant risk factors, was not significant for predicting osteoporosis at any site.

**AUC Values**

The "ability" to correctly classify patients as osteoporotic or nonosteoporotic, as defined by BMD T-scores, was based on the guidelines for interpreting AUC values used by Kent et al (14). The derived AUC values are presented in Table 2. For the prediction of low BMD (T-score ≤ -2.5) at the lumbar spine, femoral neck, and total hip, the assessment tools based exclusively on risk factors yielded AUC values in the moderate to good range (0.79–0.85). When QUS measurements were added the AUC values increased. Where BUA or VOSCAL was included the AUC values were good to excellent (0.82–0.93), which was significantly greater for the femoral neck and total hip than risk factors alone (p < 0.05). For assessment tools, which included SOSDR and SOSMT, the AUC value was within the good range (0.78) for the lumbar spine. When QUS variables were used independently the AUC values varied between poor (0.59 for SOSMT at the lumbar spine which was not significantly different from AUC value of 0.50) to excellent (0.90 for BUA at the femoral neck and total hip; and VOSCAL at the total hip).

**Specificity, PPV, and NPV**

The specificity, PPV and NPV of the assessment tools, which use only risk factors are presented in Table 3. Specificity varied from 0.32 for the lumbar spine to 0.66 for the total hip. The PPV varies from 0.21 to 0.25, whereas NPV varied from 0.94 to 0.99.

Also presented in Table 3 are the specificity, PPV and NPV of the best performing assessment tools, which combine a QUS measurement and risk factors. Specificity, PPV and NPV for these assessment tools are higher than or equal to the values of tools where only risk factors are used.

**Simplified Assessment Tools Using Risk Factors**

The simplified assessment tools using only risk factors of Table 3 are presented in Table 4. The AUC (95% confidence interval [CI]) values for these 3 simplified tools are 0.79 (CI: 0.71–0.87) for the lumbar spine, 0.85 (CI: 0.77–0.92) for the femoral neck, and 0.85 (CI: 0.76–0.93) for the total hip. These are, in general, the same as the AUC values of the original multivariable equations. At the cutoff points (set for a sensitivity of at least 0.90) the corresponding specificities were 0.28, 0.45, and 0.68, respectively. The PPV were 0.24, 0.21, and 0.22 with corresponding NPV of 0.92, 0.97, and 0.99 for the lumbar spine, femoral neck, and total hip, respectively. The ROC curves for these tools are shown in Fig. 1A.

**Simplified Assessment Tools Using Risk Factors and QUS Measurements**

The simplified assessment tools, which also include a QUS measurement, as per Table 3, are shown in Table 5. The AUC (95% CI) values for these simplified indices are as follows: 0.81 (CI: 0.74–0.89) for the lumbar spine, 0.91 (CI: 0.87–0.96) for the femoral neck, and 0.91 (CI: 0.87–0.96) for the total hip. The cutoff values stated in Table 5 ensure a sensitivity of 0.90 and result in specificities of 0.44, 0.78, and 0.84, respectively. The PPV and NPV for the tools were 0.30 and 0.90, 0.41 and 0.98, and 0.37 and 0.99. ROC curves for these tools are shown in Fig. 1B.

**Discussion**

**Risk Factors and QUS**

The use of a simple assessment tool based on patient information, collected using the Risk Factors Measurement questionnaire, and a single QUS measurement has a good to excellent ability to correctly categorize patients as having a high risk of osteoporosis or being within the normal BMD range. At the femoral neck and total hip the AUC values were significantly (p < 0.05) higher than when only risk factors were used and the specificities of these tests are high. 0.78 and 0.84. These values support the theory that a simple tool may indeed be used clinically to determine which patients require further investigation using DXA, while discounting those at low risk. Although the AUC for classifying patients as high risk, or low risk, at the lumbar spine was good at 0.82, the specificity of this test was low 0.44. The AUC for was only slightly significantly (p = 0.16) greater when QUS was added to risk factors, which may suggest that QUS is interrelated with those risk factors.

It can be seen from these results that a combination of questionnaire information and a QUS measurement perform better than when each are used individually (Fig. 2 A, B).

**Risk Factors**

The simplified assessment tools based entirely on questionnaire responses identify age, weight, NTF, and HRT as the most significant risk factors for predicting osteoporosis at the lumbar spine, femoral neck, and total hip. It can be seen from Tables 4 and 5 that the chosen risk factors have differing weights depending on the site of DXA measurement. This is expected, as there is no reason why these risk factors should explain the variability of the DXA T-scores to the same degree at all sites. The identified risk factors agree with those chosen by other groups: osteoporosis self-assessment tool (OST) (2), simple calculated osteoporosis risk estimation (SCORE) (3), osteoporosis risk assessment instrument (ORAI) (4), osteoporosis index of risk (OSIRIS) (5), ABONE (A, age; B, bulk; and ONE, or never estrogens) (6), and osteoporosis prescreening risk assessment (OPERA) (7) include some or all of these risk factors in one way or another.
Table 2

<table>
<thead>
<tr>
<th>Models based on</th>
<th>Lumbar spine (95% CI)</th>
<th>Femoral neck (95% CI)</th>
<th>Total hip (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors</td>
<td>0.79 (0.71–0.87)*</td>
<td>0.85 (0.78–0.92)*</td>
<td>0.85 (0.77–0.92)*</td>
</tr>
<tr>
<td>Questionnaire and BUA</td>
<td>0.82 (0.75–0.89)**</td>
<td>0.91 (0.87–0.96)**</td>
<td>0.91 (0.86–0.96)**</td>
</tr>
<tr>
<td>Questionnaire and VOSCAL</td>
<td>0.82 (0.74–0.89)**</td>
<td>0.92 (0.87–0.96)**</td>
<td>0.93 (0.89–0.97)**</td>
</tr>
<tr>
<td>Questionnaire and SOSDR*</td>
<td>0.78 (0.70–0.87)*</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Questionnaire and SOSMT**</td>
<td>0.78 (0.69–0.87)*</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>BUA</td>
<td>0.79 (0.72–0.85)</td>
<td>0.90 (0.84–0.96)</td>
<td>0.90 (0.84–0.96)</td>
</tr>
<tr>
<td>VOSCAL</td>
<td>0.75 (0.67–0.83)</td>
<td>0.87 (0.81–0.93)</td>
<td>0.90 (0.84–0.96)</td>
</tr>
<tr>
<td>SOSDR*</td>
<td>0.72 (0.63–0.80)</td>
<td>0.78 (0.70–0.87)</td>
<td>0.78 (0.68–0.87)</td>
</tr>
<tr>
<td>SOSPP*</td>
<td>0.68 (0.60–0.77)</td>
<td>0.72 (0.63–0.82)</td>
<td>0.72 (0.60–0.83)</td>
</tr>
<tr>
<td>SOSMT**</td>
<td>0.59 (0.47–0.71)</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Abbr: AUC, area under the curve; CI, confidence interval; BUA, broadband ultrasound attenuation; VOSCAL, velocity of sound across the calcaneus; SOSDR, speed of sound at the distal radius; NS, not significant; SOSMT, speed of sound at the midshaft tibia; SOSPP, speed of sound at the proximal phalanx of the middle finger.

*Significantly different from tool based on risk factors alone (p = 0.16); **Significantly different from tool based on risk factors alone (p < 0.05).

*Age, weight, NTF, HRT; "BUA, weight, NTF, HRT; "BUA, age, weight, NTF; 4Weight, height, NTF, HRT; "VOSCAL, age, weight, NTF; 5Sample size of 227; 6SOSDR, weight, NTF, HRT; 6Sample size of 172; 7SOSMT, age, weight, NTF, HRT; 7Sample size of 233.

Comparison with OSIRIS

OSIRIS in particular uses the same risk factors as those identified in this study. This tool was developed to predict osteoporosis at any of the frequently investigated DXA measurement sites: lumbar spine, femoral neck, and total hip (5). This concordance reinforces the theory that these risk factors are indeed the most influential for predicting risk of osteoporosis in a postmenopausal Caucasian population.

The most noticeable difference between the 2 samples is the mean age. Ben Sedrine et al (5) used a cohort with a mean age of 67.1 ± 5.2 yrs. The mean age of the sample in the present study was 59.7 ± 10.8 yrs, suggesting that the use of these risk factors may be applicable for predicting osteoporosis in a broader age range.

For comparison of the 2 tools OSIRIS was used on those aged between 60 and 80 yrs (n = 104) (criteria for inclusion in OSIRIS development). ROC analysis demonstrated an AUC value of 0.80 with a specificity of 0.36. This compares to a specificity of 0.32 at the lumbar spine, 0.44 at the femoral neck and 0.66 at the total hip, for the newly developed assessment tools. Although OSIRIS is more general, attempting to predict those at high risk of osteoporosis at any of the 3 sites, specificity at each site may be diminished to increase simplicity.

Table 3

<table>
<thead>
<tr>
<th>Site</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td>Risk factors*</td>
<td>0.92</td>
<td>0.32</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>Risk factors and QUS*</td>
<td>0.90</td>
<td>0.49</td>
<td>0.29</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>Risk factors*</td>
<td>0.91</td>
<td>0.44</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>Risk factors and QUS*</td>
<td>0.91</td>
<td>0.79</td>
<td>0.42</td>
</tr>
<tr>
<td>Total hip</td>
<td>Risk factors*</td>
<td>0.91</td>
<td>0.66</td>
<td>0.22</td>
</tr>
<tr>
<td></td>
<td>Risk factors and QUS*</td>
<td>0.91</td>
<td>0.84</td>
<td>0.33</td>
</tr>
</tbody>
</table>

*Abbr: PPV, positive predictive value; NPV, negative predictive value; QUS, quantitative ultrasound.

*Age, weight, NTF, HRT; "BUA, weight, NTF, HRT; "VOSCAL, age, weight, NTF.

Comparison with Other Risk Factor Based Assessment Tools

The OST tool uses age and weight as predictors of low BMD at the femoral neck of a postmenopausal Japanese population. The present study found that NTF and HRT are also significant for a Caucasian population. The specificity of OST was found to be 0.45 (2), which was identical to that found for predicting low BMD at the femoral neck in a Caucasian population in the current study.

Both ORAI and SCORE were developed to classify patients as either low BMD (T-score ≤ −2.0) or normal (T-score > −2.0) and are therefore not directly comparable with the newly developed indices. The ABONE assessment tool suggests that all patient over the age of 65 who weigh less than 140 lb at menopause or those who have used estrogen for less than 6 months be screened for osteoporosis (6). This would mean large numbers of people requiring DXA scanning. This is demonstrated by the specificity of 0.48, at a sensitivity of 0.83, found by Cadarette et al (15). Of these
Table 4
Simplified Indices Using Risk Factors Measurement
Questionnaire Responses

<table>
<thead>
<tr>
<th>Site</th>
<th>Simplified index</th>
<th>Score (example)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td>+ (Weight ÷ 10)</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>− (Age ÷ 10)</td>
<td>−7.9</td>
</tr>
<tr>
<td></td>
<td>− 2(NTF)</td>
<td>−2</td>
</tr>
<tr>
<td></td>
<td>+ 2(HRT)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Total score (cutoff = 3.05)</td>
<td>−3.2</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>+ (Weight ÷ 10)</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>− (Age ÷ 10)</td>
<td>−7.9</td>
</tr>
<tr>
<td></td>
<td>− (NTF)</td>
<td>−1</td>
</tr>
<tr>
<td></td>
<td>+ (HRT)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Total score (cutoff = 1.15)</td>
<td>−2.2</td>
</tr>
<tr>
<td>Total hip</td>
<td>+ (Weight ÷ 10)</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>− (Age ÷ 10)</td>
<td>−7.9</td>
</tr>
<tr>
<td></td>
<td>− (NTF)</td>
<td>−1</td>
</tr>
<tr>
<td></td>
<td>+ (HRT)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Total score (cutoff = 0.12)</td>
<td>−2.2</td>
</tr>
</tbody>
</table>

*Abbr.:* NTF, nontraumatic fracture; HRT, hormone replacement therapy.

Age (yrs); Weight (kg); NTF: 1 for history of NTF, 0 for no history of NTF; HRT: 1 for HRT use, 0 for no use of HRT.

As an example, the outcome for a patient (age 79 yrs; weight 67 kg; with history of NTF) with BMD T-score ≤ 2.5 at all 3 sites is shown in the Score column. The predicted scores based on this tool are −3.2 for the lumbar spine, −2.2 for the femoral neck, and −2.2 for the total hip. All of these are below the suggested cut off levels giving the same verdict as the BMD scores and indicating low BMD at the 3 sites.

Previously developed assessment tools, OST was seen to have the highest specificity for an English sample (9).

Another tool developed specifically for a Caucasian population is OPERA (7). It was developed in order to predict low bone density at the lumbar spine or femoral neck for a postmenopausal Italian sample. Based on Content Validity Indices, the most influential risk factors were selected. Age ≥ 65 yrs, weight < 57 kg, history of minimal trauma after 45 yrs, and steroid use for greater than 6 months all had Content Validity Indices, which were considered high enough for inclusion. High specificities (0.64 for the lumbar spine and 0.61 for the femoral neck) support the use of this simple tool for stratifying individuals as high risk or low risk. The present study agrees in part, choosing age weight and history of nontraumatic fracture as predictors, with this selection but suggests that adding a QUS measurement may improve the predictive ability above this level.

Comparison with Other Risk Factor and QUS-Based Models

Clinical risk factors and QUS have been combined to predict osteoporosis in 2 other studies that the authors are aware of. Richy et al (12) developed the ORACLE tool based on Ultrasound Bone Profile Index, age, body mass index (BMI), HRT, and NTF after the age of 45 yrs to predict osteoporosis at the femoral neck. Ultrasound Bone Profile Index was developed by Wüster et al (16) and is a score based on the dynamics of the ultrasound, signal, fast wave amplitude, and time frame of the trace. The specificity found by the authors for ORACLE (0.50) was lower than that of the assessment tool developed in the current study for prediction of osteoporosis at the femoral neck using risk factors and BUA (0.78) for the femoral neck (both at sensitivity > 0.90).

In a similar study Pongchaisayakul et al (13) combined age, weight, and QUS at the calcaneus to predict osteoporosis in Thai postmenopausal women. The researchers compared the use of age and weight, QUS, and a combination of both in an attempt to predict osteoporosis at the femoral neck. They determined that the combination model had a significantly higher AUC value than either of the other tools. Similar trends were noted in the present work where combination models outperformed models based on a single technique.
### Table 5
Simplified Indices Using Information Acquired from Risk Factors Measurement Questionnaires and QUS Measurements

<table>
<thead>
<tr>
<th>Site</th>
<th>Simplified index</th>
<th>Score (example)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine</td>
<td>+ (BUA + 10)</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>+ (Weight + 10)</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>- 2 (NTF)</td>
<td>-2</td>
</tr>
<tr>
<td></td>
<td>+ (HRT)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Total score (cutoff = 13.65)</td>
<td>7.8</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>+ (VOSCAL - 1400)</td>
<td>145.5</td>
</tr>
<tr>
<td></td>
<td>+ 3 (Weight)</td>
<td>165</td>
</tr>
<tr>
<td></td>
<td>- (Age)</td>
<td>-55</td>
</tr>
<tr>
<td></td>
<td>- 25 (NTF)</td>
<td>-25</td>
</tr>
<tr>
<td></td>
<td>Total score (cutoff = 278)</td>
<td>230.5</td>
</tr>
<tr>
<td>Total hip</td>
<td>+ (VOSCAL - 1400)</td>
<td>145.5</td>
</tr>
<tr>
<td></td>
<td>+ 3 (Weight)</td>
<td>165</td>
</tr>
<tr>
<td></td>
<td>- (Age)</td>
<td>-55</td>
</tr>
<tr>
<td></td>
<td>- 25 (NTF)</td>
<td>-25</td>
</tr>
<tr>
<td></td>
<td>Total score (cutoff = 250)</td>
<td>230.5</td>
</tr>
</tbody>
</table>

*Abbr.: QUS, quantitative ultrasound; BUA, broadband ultrasound attenuation; NTF, nontraumatic fracture; HRT, hormone replacement therapy; VOSCAL, velocity of sound across the calcaneus. Age (yrs); weight (kg); NTF: 1 for history of NTF, 0 for no history of NTF; HRT: 1 for HRT use, 0 for no use of HRT; VOSCAL (m/s); BUA (dB/MHz). As an example, the outcome for a patient (age 55 yrs; weight 55 kg; with history of NTF) with BMD T-score < 2.5 at all 3 sites is shown in the Score column. The predicted scores based on this tool are 7.8 for the lumbar spine, 230.5 for the femoral neck, and 230.5 for the total hip. All of these are below the suggested cutoff levels giving the same verdict as the BMD scores and indicating low BMD at the 3 sites.

The current study suggests that BUA at the calcaneus along with age, weight, and NTF are the most significant for a Caucasian sample. The difference in AUC and the increased specificity of the new index suggest that the BUA at the calcaneus explains more of the variability of the BMD at the femoral neck than Ultrasonic Bone Profile Index at the proximal phalanx. This may be explained, in part at least, by the composition of the 2 sites. The cancellous bone in the calcaneus may react to skeletal changes more rapidly than the cortical bone of the proximal phalanx.

**QUS**

The use of QUS as a means of predicting osteoporosis or low BMD has been investigated in depth in previous studies (8-11). BUA and VOS measured at the calcaneus have been shown to correlate with BMD in the past (9, 11, 17-19). SOS at other skeletal sites such distal radius, proximal phalanges, and midshaft tibia have also shown a significant correlation with BMD (9, 17, 20).

In particular Cook et al (17) compared the CUBA Clinical and the Sunlight Omniscense on a postmenopausal English population. They found that the CUBA Clinical had the highest AUC value of the 2 devices. It is therefore hardly surprising that measurements from this device feature in the derived assessment tools in the present study.

It is also worth noting that in some combination models, no QUS variable was selected using stepwise regression. This may be explained by the fact that if certain variables explain much of the variability of the BMD, and some variables interrelate, these will not be included. This may explain why the combination models for the total hip and femoral neck did not select SOSD or SOSMT.

**Which Site Is Better?**

Much of the morbidity associated with osteoporosis is fractures at the hip or lumbar spine. Nevitt et al (21) examined BMD from a variety of skeletal sites and compared the relative risk of hip fracture. They found that measurements from the hip showed the highest relative risk per standard deviation decrease of BMD. Similarly, Cummings et al (22)
compared the risk of vertebral fracture based on changes in BMD at the hip and at the lumbar spine. They found that a reduction of 1 standard deviation of BMD at either site resulted in the same relative risk of vertebral fracture.

Based on these values it appears that DXA scanning of the hip is a good site for monitoring skeletal bone quality and subsequent risk of osteoporotic fracture. The assessment tools developed here which use patient risk factors and QUS measurements show good specificities for predicting osteoporosis at the hip (0.84 at the total hip and 0.78 at the femoral neck).

Consequently, if clinical decisions are based on findings at the hip, the use of the assessment tools developed here could assess those who require immediate investigation.

Although specificity of the analogous assessment tool for lumbar spine was low (0.44), there may not be a need to use this if diagnosis of osteoporosis at the hip will suffice.

Therefore, the use of these assessment tools could help screen large numbers of patients and recommend individuals who require immediate investigation while rejecting those who do not need examination at present.

Limitations

Due to the fact that the sample used comprises those already referred to the DXA scanning clinic, the authors recognize the possibility that the BMD T-scores average values seen have been below the mean for their peers in the general population. To determine if the densitometric results of the selected sample were lower than would be expected if it were chosen at random, the Z-scores were studied. Simple single sample t-tests showed that the Z-scores for the lumbar spine and femoral neck were not significantly statistically different from 0, implying that the sample chosen was not an overly pessimistic reflect of the population. Single t-test analysis of the hip Z-scores showed that the mean was greater than 0 ($p = 0.003$).

Although the sample used was relatively small ($n = 235$), its size suffices to create a valid model (as shown by comparing it to the output of other tools and by using for certain subset of patients). It also gives us information as to the possible risk factors and QUS measurements that are most influential in identifying postmenopausal Caucasian women at risk of osteoporosis. We believe that further validation and analysis of the potential benefits of these assessment tools is required.

There is a fine balance between an over simplified tool and one that performs better. It could be argued that the ultimate goal is to create a very simple tool that can classify people as osteoporotic or nonosteoporotic. However, we believe that the extra specificity of this tool, due to the lack of over simplification, is warranted. Rud et al (23) studied the consequences of using OST, SCORE, and ORA1 to predict osteoporosis at the site which they were intended to be used, and the lowest DXA value of the lumbar spine, femoral neck, and total hip for peri- and early postmenopausal women. When used as designed only the OST achieved the desired sensitivity of 0.90, with a specificity of 0.70. However, when this decision rule was extended to predict osteoporosis, defined as a T-score of $\leq -2.5$ at any site, a new cutoff threshold of $<-5$ generated a sensitivity $\geq 0.90$ (0.94) whereas specificity dropped to 0.23.

Conclusions

These results suggest that an assessment tool based on risk factors and a single QUS measurement may be used to prioritize efficiently those who require DXA scanning. The high specificities found for the developed assessment tools also indicate that many unnecessary DXA investigations may be avoided. The overall results would be to relieve pressure on current resources and to ensure their more efficient use in the future.

Acknowledgments

Support has been provided by the UK Department of Transport under the BOSCONS project, which allowed us to gain access and make use of the Sunlight Omnisense and CUBA Clinical systems. Special thanks are due to all members of the Department of Radiology of GWH in Swindon UK for their generous help with this study.

References

11. Kung AWC, Ho AYY, Ben Sedrine W, et al. 2003 Comparison of a simple clinical risk index and quantitative bone ultrasound for
identifying women at increased risk of osteoporosis. Osteoporosis Int 14:716–721.
Performance when using an independent validation sample

We used stepwise regression to calculate the independent variables which could be used to predict the DXA T-scores at the lumbar spine, femoral neck and the total hip. We created models based on a development sample (n=200) and tested these on a validation sample (n=35).

The two samples were statistically not different.

Validation Sample

We then used the cut-off value above and found a specificity of 0.37 at a sensitivity of ≥0.90.

Using risk factors and QUS:
The independent variables chosen were BUA, weight, non-traumatic fracture and history of HRT.

Development Sample
For the development sample we found:
AUC = 0.79 (CI: 0.70, 0.87);

1. Lumbar Spine:
Using only risk factors:
The risk factors chosen were age, weight, non-traumatic fracture and history of HRT.

Development Sample
AUC = 0.76 (CI: 0.67, 0.85).
For a sensitivity of ≥ 0.90 the specificity was found to be 0.27 at a cut-off of -0.7552.
For a sensitivity of $\geq 0.90$ the specificity was found to be 0.44 at a cut-off of -0.9903.

**Validation Sample**

We then used the cut-off value above and found a specificity of 0.48 at a sensitivity of $\geq 0.9$.

### 2. Femoral Neck:

**Using only risk factors:**
The risk factors chosen were age, weight, non traumatic fracture and history of HRT.

**Development Sample**

For the development sample we found:
AUC = 0.82 (CI: 0.73, 0.91);
For a sensitivity of $\geq 0.90$ the specificity was found to be 0.38 at a cut-off of -1.004.

![Development ROC Curve](image)

**Validation Sample**

We then used the cut-off value above and found a specificity of 0.70 at a sensitivity of $\geq 0.9$.

### 3. Total Hip:

**Using only risk factors:**
The risk factors chosen were age, weight, non traumatic fracture and history of HRT.

**Development Sample**

For the development sample we found:
AUC = 0.82 (CI: 0.0, 0);
For a sensitivity of $\geq 0.90$ the specificity was found to be 0.51 at a cut-off of -0.7095.

**Validation Sample**

We then used the cut-off value above and found a specificity of 0.41 at a sensitivity of 1.

**Using Risk factors and QUS:**
The risk factors chosen were VOSCAL, weight, non traumatic fracture and history of HRT.
Validation Sample

We then used the cut-off value above and found a specificity of 0.50 at a sensitivity of 1.

Using risk factors and QUS:
The risk factors chosen were VOSCAL, weight, age and non traumatic fracture.

Development Sample

For the development sample we found:
AUC = 0.92 (CI: 0.87, 0.97).

For a sensitivity of ≥ 0.90 the specificity was found to be 0.72 at a cut-off of -1.155.

Validation Sample

We then used the cut-off value above and found a specificity of 0.73 at a sensitivity of ≥ 0.9.
Great Western Hospital Information Sheet
INFORMATION SHEET
Re: QUS scanning for new finger scanner prototype project

Study title
Measurement of quantitative ultrasound through the proximal phalanx.

What is the purpose of this study?
The purpose of this study is to determine the utility of the proximal phalanges (first bone of the finger) as a site for Quantitative Ultrasound (QUS) scanning. With this information it is hoped that a scanning system that investigates the proximal phalanges can be developed to get a quick, accurate description of the skeletal condition.

Study Hypothesis
Velocity of Sound (VOS) and Broadband Ultrasound Attenuation (BUA) of bone have been studied in order to determine the relationship of Quantitative Ultrasound (QUS) with bone parameters. Within the field, it is believed that VOS measurements are determined by the density and elasticity of the bone. BUA, on the other hand, is considered to depend on the density and microarchitecture.
The most studied skeletal site in terms of QUS is the calcaneus. Both the VOS and the BUA of the calcaneus have been shown to have a significant correlation with the measured Bone Mineral Density (BMD) at the spine and proximal femur. They have also displayed promising ability at differentiating between people with osteoporotics fractures and those without.
Most of the research regarding QUS measurements at the proximal phalanges concern VOS. In previous investigations, the VOS has shown a significant correlation with spinal BMD. Some researchers suggest that the recorded waveform can be divided into separate segments which represent the pathway of transmission through different structures. Given that these structures change with aging and the progression of various bone conditions, it is hypothesised that by measuring the energy of various parts of the waveform the overall skeletal condition can be predicted.

What is Bone Mineral Density (BMD)?
Bone Mineral Density (BMD) is simply a measure of mineral density in an individual’s bones. Peak BMD is reached in the third or fourth decade of life. After this peak, there is a natural decline in BMD. While this is expected, in some cases the decline in bone density occurs at a much higher rate.

What is osteoporosis?
Osteoporosis is defined as having a BMD of less than 2.5 standard deviations below the BMD of a young healthy adult at the hip or spine. Those with osteoporosis are at an increased risk of suffering a fracture, even with minimal trauma. The manifestations of the condition include thinning and weakening of the bones. Osteoporosis is a condition which affects large numbers of older people, particularly women. Unfortunately this means that more people suffer from fractures (bone breaks) as the bone weakens. We are now discovering better ways of both preventing and treating this condition, however we need better and easier means of detecting osteoporosis.

What is Quantitative Ultrasound (QUS)?
Ultrasound is a mechanical vibration that travels through a medium. The wave that propagates is altered by the material properties and the geometry of the medium. QUS is the measuring of the specific parts of the wave in order to quantify the effect of the medium
Appendix D

MMU Ethical Approval Application
Application for Ethical Approval for the Use of Humans in Research

In designing research involving humans, investigators should be able to demonstrate that the research is based on sound scientific principles. These criteria will be considered by the Ethics Committee before approving a project. Please note that ethical approval for studies that involve clinical populations will not be granted unless accompanied by a letter granting ethical approval from the appropriate regional health authority ethics committee. All of the following details must be provided and answered under each subheading, preferably typewritten or word-processed.

1. Name of responsible investigator(s).
   - Dr. Keith Winwood
   - Dr. Peter Zioupos (DMAS Cranfield University)
   - Mr. Enda Minnock (PhD research student, DMAS Cranfield University)

2. Title of investigation.
   Bone density of the finger (proximal phalange) using peripheral quantitative computed tomography (pQCT) scanning and subsequent comparison with Quantitative Ultrasound (QUS) with other peripheral site measurements.

3. Is this:
   (a) a teaching exercise?
   (b) an undergraduate project?
   (c) a post-graduate (e.g. M.Sc.) taught project?
   (d) a staff or PhD programme research project?

   Staff research project in corporation with Cranfield University for completion of a final grant report in May 2007 which will also possibly lead to future collaborative grant applications.

4. Have the full details of the procedure been appended: Yes

   Please see attached Cranfield documentation and ethical permission accepted from Swindon Research Ethics Committee.

5. Provide a brief description (500 words maximum) and purpose of the investigation. This should include a rationale for the study and a statement of the hypothesis to be tested. It must include information on whether the study is collaborative, replication or new.

   This study is a collaborative project with colleagues from Cranfield University regarding a new finger prototype scanner by the use of quantitative ultrasound (QUS) technology for measurement of bone density. The purpose of this study is to gain validated density values from peripheral quantitative computed tomography (pQCT) in comparison to the obtained data from the new prototype, and for the completion of a final grant report (May 2007). The hypothesis is that data obtained from the pQCT will validate the new scanner finger prototype. The participant will have a pQCT of the proximal phalange and have an ultrasound scan of the finger, wrist, tibia, and calcaneus by both a CUBA Clinical (McCUE PLC) and Sunlight Omnisense (Sunlight Ultrasound Technologies Ltd.). The ultrasound equipment is commercial and portable and will be transported and operated by Enda Minnock (PhD student, Cranfield University) at the Alsager campus for a period of approximately 2-3 days. The results are to validate a new prototype scanner for a final grant report, thus if valid may create future grant applications with both
institutions. (Please see attached information from Cranfield University and ethical acceptance from there institute).

6. (a) How will the participants be recruited?

The participants will be recruited from a previous study conducted by Dr. K Winwood (smoking study) who said that they would be available for future studies, as well as from the university campus.

(b) Provide details on the number and type of participants likely to be involved?

We require just approximately 10-20 people aged over the age of 18 from a spectrum of age ranges to validate the density values obtained with the new finger scanner prototype in relation to density values obtained by peripheral quantitative computed tomography (pQCT)

(c) What inclusion and exclusion criteria will be employed in the selection of participants?

Participants must be over the age of 18 years and not taking any medication that is known to effect bone metabolism.

(d) What criteria have been employed to determine the number of participants for the study?

The participants are just required for the validation of the new finger scanner prototype (please see above).

7. Likely duration of project and location of study.

The duration of the study is for a 2-3 day period where Enda (Cranfield PhD student) will scan by the use of ultrasound the participants by both the commercially available ultrasound and the new prototype. Dr Keith Winwood will scan the participants by pQCT. The equipment will be located in the Harold Frost Laboratory (pQCT machine) and the ultrasound will be brought up from Cranfield University where full ethics have been accepted (please see attached).

8. Specify the particular procedures that involve human participants.

A bone scan will be obtained by the use of a pQCT by the Stratec XCT 2000 scanner (Stratec Medizintechnik GmbH, Pforzheim, Germany) of the first phalange, this will be operated by Dr Keith Winwood.

An ultrasound scan (QUS) will be obtained of the participant at the proximal phalange, tibia, wrist and calcaneus. This involves the participant remaining sitting comfortably whilst a scan takes place, no discomfort or pain is occurred to the participant please see information from Cranfield University (attached). This procedure will be preformed by Mr Enda Minnock (Cranfield University).

The participant will be asked to fill out a questionnaire regarding items related to osteoporosis and health that has been previously used at a previous study at Cranfield.

9. Are any novel procedures involved in this study? If so, full details must be attached.

There are no new novel procedures endorsed within this study.

10. Clearly state all substances or materials to be administered or applied. State their potential hazards, if any, and the precautions to be taken.
The only item that will be applied to the participant is a manufacturer’s conductive gel for the ultrasound procedure. This will be applied to the area going to be scanned, no potential hazard will be involved.

For the pQCT scan however there is a potential risk of exposure to radiation that has to be considered within this study. A single pQCT bone scan has an expected radiation dose of approx. 0.9 µSievert per scan. In comparison a return flight to the Canary Islands is approx. 80µSievert and the annual natural exposure being 2400 µSievert, the received dose is very low. The XCT 2000 is CE certified and is safe regarding electrical and mechanical risks for the participants.

11. State the degree of discomfort in terms of apprehension, pain, stress and disturbance in terms of alteration to routine.

There will be no degree of discomfort, apprehension, pain, stress, or disturbance in terms of alteration to routine for any of the participants.

12. State your experience or that of the supervisor or other investigators in this type of investigation.

I have previously had a vast amount of experience at Manchester Metropolitan University regarding pQCT both with undergraduate, post graduate, and research studies (Miss D.Wilks study’s, Smoking study, and Dancers study). I also went on a course regarding ionising radiation and pQCT. Both Enda Minnock and Dr Peter Zioupos have had several years experience in ultrasound technology and Peter had a PhD student complete his thesis within this area Dr Richard Cook (University of Dunedin, New Zealand) within this subject area (Recent papers below).


Ethics proposals have also been completed and accepted at Cranfield University for ultrasound (Please see attached Faxes from Dr David Collins Consultant Rheumatologist: Swindon Research Ethics Committee).

13. You must indicate clearly that the participant's informed consent will be obtained and, where necessary, in the presence of a parent (for minors only). You must also attach a sample of the informed consent form (typewritten) which will be presented to participants (Appendix IV). In the case of participants with learning difficulties, you must state the procedures that have been undertaken to ensure that the consent is, indeed, informed consent.

All participants will complete an informed consent form for both MMU and Cranfield University (See attached for both establishments).

14. How and where is the data to be stored?

The data will be stored on a password controlled PC by both institutions; all data will be anonymised for QUS scans.
Will the data be securely stored?
Yes

Where?
On password controlled PC’s that are only used by the investigators.

Will information which could identify participants be coded?
Yes (see above)

Will the data be destroyed at the end of the study?
No the data will not be destroyed due to the investigators own interest. However it will be securely stored and all back up will be locked away in a safe place.
Appendix IV

Informed Consent Form (to be retained by the investigator for MMU)

Participant:

Name:    Sex: Male / Female

Date of Birth:

Supervisor/Principal Investigator: Dr Keith Winwood (Manchester Metropolitan University)

Investigator/Collaborators: Dr Peter Zioupos (DMAS, Cranfield University), Mr Enda Minnock (PhD Research Student, DMAS, Cranfield University)

Ethics Committee Approval Number:

Project Title: Bone density of the finger (proximal phalange) using peripheral quantitative computed tomography (pQCT) scanning and subsequent comparison with Quantitative Ultrasound (QUS) with other peripheral site measurements.

Purpose of study and brief description of procedures.

The purpose of the study is to determine the utility of the proximal phalanges (first bone of the finger) as a site for a new Quantitative Ultrasound (QUS) scanning prototype in collaboration with Cranfield University. With this information it is hoped that a scanning system that investigates the proximal phalanges can be developed to get a quick, accurate description of the condition of the skeleton. You will be asked to sit comfortably and have your fingers scanned by peripheral quantitative computed tomography (pQCT) to obtain your bone density for validation of the new QUS device. You will then have your finger, tibia, wrist and calcaneus bone scanned by a commercially QUS device. Finally you will be asked a short questionnaire of which all information obtained will be treated confidentially.

Participant Statement.

I fully understand what is involved in taking part in this study. Any questions I have about the study, or my participation in it, have been answered to my satisfaction. I understand that I do not have to take part and that I may decide to withdraw from the study at any point without prejudice. I have had my attention drawn to the document ‘Ethical Regulations for the Use of Humans in Research’. My concerns regarding this study have been answered and such further concerns as I have during the time of the study will be responded to. It has been made clear to me that, should I feel that these Regulations are being infringed or that my interests are otherwise being ignored, neglected or denied, I should inform the Chair of the Ethics Committee of the Department of Exercise and Sport Science, Manchester Metropolitan University, Hassall Road, Alsager, Cheshire, ST7 2HL who will undertake to investigate my complaint.

Signed ........................................................................ Date ................................

I certify that the details of this study have been fully explained and described in writing to ................................................., and have been understood by him/her and that I consent to his/her participation in this study.

Signed ........................................................................ Date ................................
CONSENT FORM

Title Project:
Bone density of the finger (proximal phalange) using peripheral quantitative computed tomography (pQCT) scanning and subsequent comparison with Quantitative Ultrasound (QUS) with other peripheral site measurements.

Name of Researchers:

Mr. Enda Minnock, Doctoral Researcher, DMAS, Cranfield University
Dr. Peter Zioupos, Senior Lecturer, DMAS, Cranfield University
Dr. Keith Winwood, Institute for Biophysical & Clinical Research into Human Movement, Manchester Metropolitan University

1. I confirm that I have read and understand the information sheet dated 22 Mar. 07 (version 1.0) for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time giving any reason.

3. I understand that I will be asked questions from a questionnaire. I also understand that I will have a scan of my heel bone.

4. I agree to take part in the above study.

_____________________________ ___________________ ___________________
Name of Volunteer Date Signature

_____________________________ ___________________ ___________________
Name of person taking consent (if different from researcher) Date Signature

_____________________________ ___________________ ___________________
Researcher Date Signature
Appendix E

MMU Information and Consent Form
INFORMATION SHEET
Re: pQCT trials and QUS scanning for new finger scanner prototype project

Study title
Simulated passage of ultrasound through the finger using pQCT scanning, and subsequent comparison with Quantitative Ultrasound measurements of the heel bone

What is the purpose of this study?
The purpose of this study is to determine the utility of the proximal phalanges (first bone of the finger) as a site for Quantitative Ultrasound (QUS) scanning. With this information it is hoped that a scanning system that investigates the proximal phalanges can be developed to get a quick, accurate description of the condition of the skeleton.

Study Hypothesis
Velocity of Sound (VOS) and Broadband Ultrasound Attenuation (BUA) of bone have been studied in order to determine the relationship of Quantitative Ultrasound (QUS) with bone parameters. Within the field, it is believed that VOS measurements are determined by the density and elasticity of the bone. BUA, on the other hand, is considered to depend on the density and microarchitecture.
The most studied skeletal site in terms of QUS is the calcaneus. Both the VOS and the BUA of the calcaneus have been shown to have a significant correlation with the measured BMD at the spine and proximal femur. They have also displayed promising ability at differentiating between people with osteoporotics fractures and those without.
Most of the research regarding QUS measurements at the proximal phalanges concern VOS. In previous investigations, the VOS has shown a significant correlation with spinal BMD. Some researchers have investigated the amplitude of the first arriving peak of the ultrasonic wave as it crosses the proximal phalanges. It was found that this measure was correlated to the area of the medullary canal of the studied phalanges.
With aging, and the deterioration of the skeletal condition, the density and geometry of the proximal phalanges changes.
Based on this evidence, it seems that the BUA of the proximal phalanges should be correlated to the state of the bone and that the deterioration of the bone may be reflected in this measurement. It is hoped that this study will attempt to confirm this belief and also will quantify the degree to which BUA changes as the state of the bone changes.

What is Bone Mineral Density (BMD)?
Bone Mineral Density (BMD) is simply a measure of mineral density in an individuals bones. Peak BMD is reached in the third or fourth decade of life. After this peak, there is a natural decline in BMD. While this is expected, some people lose bone density a higher rate than others.

What is osteoporosis?
Osteoporosis is defined as having a BMD of less than 2.5 standard deviations below the BMD of a young healthy adult at the hip or spine. Those with osteoporosis are at an increased risk of suffering a fracture, even with minimal trauma. The manifestations of the condition include thinning and weakening of the bones. Osteoporosis is a condition which affects large numbers of older people, particularly women. Unfortunately this means that more people suffer from fractures (bone breaks) as the bone weakens. We are now discovering better ways of both preventing and treating this condition, however we need better and easier means of detecting osteoporosis.
What is Quantitative Ultrasound (QUS)?
Ultrasound is a mechanical vibration that travels through a medium. The wave that propagates is altered by the material properties and the geometry of the medium. QUS is the measuring of the specific parts of the wave in order to quantify the effect of the medium (in this case bone). There has been much research at the calcaneus and as a result there are a number of commercially available QUS scanning systems such as the CUBA Clinical (McCUE PLC) and the Achilles+ (Lunar). A multi-site scanning system is also available to measure VOS along the cortex of certain bones, the Sunlight Omnisense (Sunlight Ultrasound Technologies Ltd.). Research at the proximal phalanges to date has focussed on the through VOS, with one commercially assessment tool, the DBM Sonic (IGEA).

Why have I been chosen?
You have been chosen because you have volunteered to take part.

Who is organising the study?
The study is being organised by Cranfield University in association with Manchester Metropolitan University. This study will take place over the next three months.

What will happen to me if I take part?
You will be asked to complete a questionnaire relating to your health and lifestyle. You will also be scanned at the heel bone with a commercially available QUS device, the CUBA Clinical. This is a completely non-invasive procedure and is painless.

Are there any disadvantages in taking part in this study?
There are no disadvantages in taking part in this study. If your change you mind you can withdraw at any time without saying why.

What are the possible risks of taking part in this study?
There are no risks at all involved in taking part in this study.

What are the possible benefits of taking part in this study?
If the scan gives any cause for concern you will be informed.

Confidentiality – Who will know that I am taking part in the study?
Only the research team will be able to identify you from your questionnaire and scan results. All data will be anonymised so that the researchers who are outside the research team will not be able to identify you.

Who has reviewed the study?
The Manchester Metropolitan Ethics Committee has approved this study.

Research in the centre to date
Research in the centre to date has focussed on the comparison of a number of skeletal sites in order to determine which if any are the most representative of the overall skeletal condition. There has also been some research into using questionnaires as a possible screening tool for osteoporosis. If you would like further information please see:
What will happen to the results of this study?
If you would like to be sent a short summary of the results of this study, we would be only
too delighted to send one to you. If there is any further information that you require please
call Enda Minnock (01793) 785531 or email e.b.minnock@cranfield.ac.uk.
CONSENT FORM

Title Project: Simulated passage of ultrasound through the finger using pQCT scanning, and subsequent comparison with quantitative ultrasound measurements of the heel bone

Name of Researchers:

Enda Minnock, Doctoral Researcher, DMAS, Cranfield University
Dr Peter Zioupos, Senior Lecturer, DMAS, Cranfield University
Dr Keith Winwood, Institute for Biophysical & Clinical Research into Human Movement, Manchester Metropolitan University

1. I confirm that I have read and understand the information sheet dated for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time giving any reason.

3. I understand that I will be asked questions from a questionnaire. I also understand that I will have a scan of my heel bone.

4. I agree to take part in the above study.

Name of Volunteer Date Signature

Name of person taking consent (if different from researcher) Date Signature

Researcher Date Signature

1 for volunteer 1 for researcher 1 to be kept in the dept
Appendix F

Mechanical Drawings for Prototype Scanner
NOTE
BREAK SHARP EDGES

1. NOTE BREAK SHARP EDGES

2. DRILL Ø 6.20

3. CSK Ø 5.2 THRU 10.4 X 90°

4. 4 X Ø 5.2 THRU CSK Ø 8.2 X 90°

5. ENDA MINNOC

6. 4 X Ø 5.2 THRU CSK Ø 10.4 X 90°

7. D.W. NO.

8. DWG NO.

9. TITLE

10. DRAWN BY

11. APPROVED BY

12. PROJECTION

13. SCALE

14. FINISH

15. MATL

16. TOLERANCES

17. DATE

18. QTY

19. SURFACE FINISH IN µm

20. UNLESS OTHERWISE STATED

21. DIMS IN mm

22. UNLESS STATED

23. GREY PVC

24. BACK PLATE

25. ROTATE.SLDDRW

26. 31/10/06

27. 5

28. 1

29. A3

30. Defence College of Management and Technology

31. Cranfield University
NOTE
BREAK SHARP EDGES

4 X \( \phi 5.2 \) CSK \( \phi 10.4 \times 90^\circ \)

10.0

180.0

225.0

10.00

160

17.00

10.0

18

GREY PVC

2

31/10/06

D.N.S.

ENDA MINNOCK

1

BOTTOM HAND PLATE
NOTE
BREAK SHARP EDGES

REAM \( \phi 8.0 \times 20.00 \text{ DEEP} \)

\( \phi 3.3 \times 15 \text{ DEEP} \)
M4 X 0.7

\( \phi 3.3 \times 12.5 \text{ DEEP} \)
M4 X 0.7

2 x \( \phi 3.3 \times 14 \text{ DEEP} \)
M4 X 0.7

NOTE BREAK SHARP EDGES

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<th>MATL:</th>
<th>TITLE:</th>
<th>QTY:</th>
<th>DATE:</th>
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<td>BAR HOLDER</td>
<td>2</td>
<td>30/10/06</td>
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<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.00 = \pm 0.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DEG \pm 1°</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>UNLESS OTHERWISE STATED</td>
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<td>BAR HOLDER.SLDDRW</td>
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</tr>
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<tbody>
<tr>
<td>ENDA MINNOCK</td>
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DEFENCE ACADEMY
OF THE UNITED KINGDOM
Cranfield UNIVERSITY
Defence College of Management and Technology
SECTION A-A

2 X Ø 4.2
CSK Ø 6 x 90°

R10.0 TYP

2 X 4.2

CSK 6 X 90

152.0
50.50
108.0
220.0
65.00
4.50
17.0
130

NOTE
BREAK SHARP EDGES

R10.0 TYP

4 X Ø 4.2 X 15.0 DEEP

A

A

B

B

3.2

DATE: SCALE:

0.00 = 0.1
DEG

UNLESS STATED

GREY PVC

TOLERANCES:

0 = 0.01
0.00 = 0.01
0.000 = 0.001
STATED

UNLESS OTHERWISE

APPROVED BY:

DRAWN BY:

COVER BOX

D.W.G NO:

QTY:

1

TYP

NOTE BREAK SHARP EDGES

R10.0 TYP

4 X Ø 4.2 X 15.0 DEEP

A

A

B

B

3.2

DATE: SCALE:

0.00 = 0.1
DEG

UNLESS STATED

GREY PVC

TOLERANCES:

0 = 0.01
0.00 = 0.01
0.000 = 0.001
STATED

UNLESS OTHERWISE

APPROVED BY:

DRAWN BY:

COVER BOX
M8 X 1.25
PART SUPPLIED MODIFY AS SHOWN
50.0
18.0
AS SUPPLIED
8
MATL: 
SLDWRKS FILE: 
A4 
AS SUPPLIED ... µm UNLESS OTHERWISE 
UNLESS STATED 
DWG NO: 0      =  1 
0.0   =  0.2 
0.00 =  0.1 
DEG   ±1° 
SURFACE FINISH IN µm UNLESS STATED
DIMS IN mm
TITLE: 
DRIVE HANDLE TOP
DEFENCE ACADEMY OF THE UNITED KINGDOM 
Cranfield UNIVERSITY
Defence College of Management and Technology
APPROVED BY: 
TOLERANCES: 
DWG NO: 8 
SLDWRKS FILE: DRIVE HANDLE TOP.SLDDRW
FINISH: AS SUPPLIED 
SCALE: D.N.S. 
0 = ± 1 
0.0 = ± 0.2 
0.00 = ± 0.1 
DEG = ±1° 
UNLESS OTHERWISE STATED 
QTY: 1 
PREPARED BY: 
DRAWN BY: ENDA MINNOCK 
DATE: 30/10/06 
3.2/ SURFACE FINISH IN µm UNLESS STATED 
0.0= 0.2
0.00= 0.1
DEG ±1° 
SURFACE FINISH IN µm UNLESS STATED 
DIMS IN mm
STEEL AS SUPPLIED
NOTE
BREAK SHARP EDGES

6.0

Φ 12.0

Φ 4.2 X 4.0 DEEP
M5 X 0.8

13

NOTE BREAK SHARP EDGES
4.2 X 4.0 DEEP
M5 X 0.8
12.0
1
01/11/06
MATL:
SLDWRKS FILE: 3.2
FINGER PAD GREY PVC

QTY:
FINISH:
DIMS IN mm

SCALE:
SURFACE FINISH IN µm UNLESS STATED
DIMS IN mm

TITLE:
FINGER PAD

APPROVED BY:
DRAWN BY:
ENDA MINNOCK

TOLERANCES:
0 = ±1
0.0 = ±0.2
0.00 = ±0.1
DEG ±1"
UNLESS OTHERWISE STATED

DWG NO:
SLDWRKS FILE:
FINGER PAD.SLDDRW

0.000 = 0.1
DEG
0.000 = 0.1
E

DEFENCE ACADEMY
OF THE UNITED KINGDOM
Cranfield UNIVERSITY
Defence College of Management and Technology

QTY:
1

DATE:
01/11/06

A4
NOTE
BREAK SHARP EDGES

2 X Ø 4.2 X 15 DEEP
M5 X 0.8

NOTE BREAK SHARP EDGES

0 = ± 1
0.0 = ± 0.2
0.00 = ± 0.1
DEG ± 1°
UNLESS OTHERWISE STATED

35.0

DIMENSIONS IN mm

30.0

30/10/06

SLDWRKS FILE: HINGE.SLDDRW

DRAWN BY: ENDA MINNOCK

APPROVED BY:

TOLERANCES:

MATL: AL ALLOY 6082 HE30

FINISH:

SCALE: D.N.S.

TITLE: HINGE

QTY: 2

DATE: 30/10/06

DEFENCE ACADEMY OF THE UNITED KINGDOM

Cranfield University

Defence College of Management and Technology
NOTE
BREAK SHARP EDGES

\[
\begin{align*}
\phi 10.1 & \text{ THRU} & \text{ R15.0} \\
5.00 & & 10.00 \\
6.00 & & 9.90 \\
30.0 & & 15.0 \\
2 \times \phi 4.2 & \times 15 & \text{ DEEP} \\
M 5 \times 0.8 & 6.00 & 5.00 \\
18 & & \\
10.00 & & \\
9.90 & & \\
0.05 & & \\
\phi 0.05 \\
\end{align*}
\]

\[2 \times \phi 4.2 \times 15 \text{ DEEP} \]

\[M 5 \times 0.8 \]

\[6.00 \]

\[5.00 \]

\[10.00 \]

\[9.90 \]

\[0.05 \]

\[\phi 0.05 \]

\[\phi 10.1 \text{ THRU} \]

\[\text{R15.0} \]

\[\text{AL ALLOY 6082 HE30} \]

\[\text{HINGE BACK.SLDDRW} \]

\[\text{MATL:} \]

\[\text{SLDWRKS FILE: 3.2} \]

\[\text{HINGE BACK 2} \]

\[1 \]

\[30/10/06 \]

\[\text{ENDA MINNOCK} \]

\[\text{QTY:} \]

\[\text{FINISH:} \]

\[\text{TOLERANCES:} \]

\[0 = \pm 1 \]

\[0.0 = \pm 0.2 \]

\[0.00 = \pm 0.1 \]

\[\text{DEG } \pm 1" \]

\[\text{UNLESS OTHERWISE STATED} \]

\[\text{DIMS IN mm} \]

\[\text{SCALE:} \]

\[\text{D.N.S.} \]

\[\text{APPROVED BY:} \]

\[\text{DRAWN BY:} \]

\[\text{DATE:} \]

\[30/10/06 \]

\[\text{DEFENCE ACADEMY OF THE UNITED KINGDOM} \]

\[\text{Cranfield UNIVERSITY} \]

\[\text{Defence College of Management and Technology} \]

\[\text{QTY:} \]

\[2 \]

\[\text{A4} \]

\[\text{SLDWRKS FILE: HINGE-BACK.SLDDRW} \]
NOTE
BREAK SHARP EDGES

ENDA MINNOCK

GREY PVC

<table>
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<th>APPROVED BY:</th>
<th>DRAWN BY:</th>
</tr>
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<tr>
<td>0 = ± 1</td>
<td>D.N.S.</td>
<td>ENDA MINNOCK</td>
</tr>
<tr>
<td>0.0 = ± 0.2</td>
<td></td>
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</tr>
<tr>
<td>0.00 = ± 0.1</td>
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<td></td>
</tr>
<tr>
<td>DEG ± 1</td>
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DATE: 01/11/06
SCALE: D.N.S.
DIMS IN mm

GTY: 1
PROJECT: A3

NOTE BREAK SHARP EDGES

KNUCKLE ADJUSTER ARM
NOTE
BREAK SHARP EDGES
IF IN DOUBT PLEASE ASK

DRAWN BY: ENDA MINNOCK

DATE: 01/11/06

SCALE: D.N.S.

TITLE: TRANSDUCER ARM - RIGHT

D.W.G. NO: 10

NOTE: DIMS IN mm

17.8
12.0
R12.5

55.0

R1.0 TYP

20.9

44.0

55.0

R67.50

R55.00

R80.00

55.00 R

88.3

80.0

21.9

22.0

5.0

3.0

20.0

12.5

5.0

25.0

R3.0 TYP

8.0

8.2

8.0

4.2

19

3.0

17.0 X 90

80.0

44.0

55.0

21.9

5

67.50

22.0

16.018

16.000

CSK Ø17.0 X 90°

NEITHER SIDE

R1.0 TYP

A3

1

TRANSDUCER ARM - RIGHT

GREY PVC

M4 X 0.7

+ Ø 0.05 A B

M2.5 X 0.45

3.3 THRU

2.2 X 8.0 DEEP

0.05 A B

NOTE BREAK SHARP EDGES
IF IN DOUBT PLEASE ASK

VIEW A

UNLESS STATED

0.0 = ±0.1

0.00 = ±0.01

0.000 = ±0.001

UNLESS OTHERWISE STATED

UNLESS STATED

0 = ±1

0.0 = ±0.02
NOTE BREAK SHARP EDGES

R10.0 TYP
6.2
6.0 TYP
6.2
36.0
105.0
43.8 TYP SLOT
R60.0 TYP
19.00
SLOT \( \phi 6.2 \)
8.0
36.0
86.0
30.0
10.0
19.0

\( \phi 6.8 \times 20.0 \) DEEP
M8 X 1.25

\( \phi 3.0 \) TYP

\( 3.2 / \sqrt{ } \) SURFACE FINISH IN \( \mu m \) UNLESS STATED

MATL: GREY PVC

TITLE: TOP SLIDER BAR

DIMS IN mm

TOLERANCES:

0 = \( \pm 1 \)
0.0 = \( \pm 0.2 \)
0.00 = \( \pm 0.1 \)
DEG \( \pm 1^\circ \)
UNLESS OTHERWISE STATED

FINISH: AS SUPPLIED

SCALE: D.N.S.

0 = 0.0 = 0.00 = 0.2
DEG = 0.1
SURFACE FINISH IN \( \mu m \) UNLESS STATED

DRAWN BY: ENDA MINNOCK

APPROVED BY:

DATE: 30/10/06

QTY: 1

A4

SLDWRKS FILE: TOP- SLIDER-BAR.SLDDRW

DWG NO: 7

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OF THE UNITED KINGDOM

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Defence College of Management and Technology
NOTE
BREAK SHARP EDGES

LOCK NUT MATERIAL:
304 STAINLESS STEEL

WASHER MATERIAL:
AL ALLOY 6082 HE30

NOTE BREAK SHARP EDGES

3.3 THRU
M4 X 0.7
8.0
7.8
4.00
5.00
10.0

CHAM 0.5 X 45° TYP

LOCK NUT & WASHER

QTY: 2 OF EACH PART

DWG NO: 12

SLDWRKS FILE: LOCK-NUT & WASHER.SLDDRW

APPROVED BY: 

DRAWN BY: ENDA MINNOCK

TOLERANCES:

0 = ± 1
0.0 = ± 0.2
0.00 = ± 0.1
DEG ± 1°
UNLESS OTHERWISE STATED

FINISH:

SCALE: D.N.S.

SURFACE FINISH IN µm
UNLESS STATED

DIMENSIONS IN mm

TITLE:
LOCK NUT & WASHER

DEFENCE ACADEMY
OF THE UNITED KINGDOM

Cranfield UNIVERSITY

Defence College of Management and Technology

DATE: 30/10/06
ESB 2008 Poster Presentation

Can Questionnaires And Quantitative Ultrasound Be Used To Screen For Osteoporosis?
Can Questionnaires And Quantitative Ultrasound Be Used To Screen For Osteoporosis?

Introduction
Osteoporosis affects millions of people every year. With the associated loss of bone and resorption of the trabeculae, the most common problem encountered is fracture of the hip, spine and wrist, even at low energy levels. If detection occurs early enough, changes to diet and lifestyle or a prescribed treatment may halt or slow down bone loss. Differing approaches have been investigated to detect osteoporosis, or those at high risk of developing it. These have tended to concentrate on simple questionnaire based models and quantitative ultrasound.

The aim of this study was to determine if combining these two approaches could improve on the predictive ability and specificity, when compared to each individual method.

Methods
DXA scans were taken at the hip and spine of 235 postmenopausal Caucasian women. All volunteers completed questionnaires covering lifestyle, exercise and medical and reproductive history. QUS measurements were taken using the CUBA Clinical and Sunlight mnisense. Correlations between all risk factors and QUS measurements and the DXA T-scores were calculated. Those significant at (P<0.2) were included as possible inputs in stepwise regression in order to find multivariate models for predicting BMD T-score at the lumbar spine, femoral neck and total hip. This created two models for predicting T-score, one using only risk factors and one using a combination of risk factors and QUS variables.

Results
Area Under the Curve (AUC) values of both newly developed tools are shown in Table 1. The AUC values of tools which predict osteoporosis at the femoral neck and total hip using risk factors and QUS were significantly greater (P<0.05) than those using only risk factors. For the lumbar spine, the AUC value of the combination tool was only slightly significantly greater (P=0.16) than the simple, risk factor based tool. The specificities were also greater when QUS was used (See Table 2).

Discussion and Conclusion
It was seen that the developed assessment tools could be used to prioritise those requiring DXA scanning. They had high sensitivity and specificity values. This would indicate that they have the potential to increase the efficiency of current DXA resources. It may also be used as a screening tool whereby large numbers of people could be scanned, leading to possible prevention of osteoporotic fractures.

Table 1: Area Under the Curve Values for Assessment Tool

<table>
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<th>Lumbar Spine</th>
<th>Femoral Neck</th>
<th>Total Hip</th>
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<td>Risk Factors</td>
<td>0.79 (0.74-0.84)</td>
<td>0.85 (0.80-0.90)</td>
<td>0.85 (0.77-0.93)</td>
</tr>
<tr>
<td>Combination of Risk Factors and QUS</td>
<td>0.82 (0.75-0.89)</td>
<td>0.93 (0.87-0.93)</td>
<td>0.93 (0.89-0.93)</td>
</tr>
</tbody>
</table>

Table 2: Specificity at Sensitivity of ≥ 90% for Assessment Tool

<table>
<thead>
<tr>
<th>Assessment Tool Based On</th>
<th>Lumbar Spine</th>
<th>Femoral Neck</th>
<th>Total Hip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Factors</td>
<td>0.32*</td>
<td>0.44*</td>
<td>0.64*</td>
</tr>
<tr>
<td>Combination of Risk Factors and QUS</td>
<td>0.49*</td>
<td>0.79*</td>
<td>0.84*</td>
</tr>
</tbody>
</table>

*Age, Weight, Nine Traumatic Fracture (NTT), Hormone Replacement Therapy (HRT)
*Broadband Ultrasound Attenuation at the Birefringent Plane (BUP)
*Velocity of Sound at the calcaneous (Age, Weight, NTT)
Appendix H

ESB 2008 Poster Presentation

Using Quantitative Ultrasound To Predict Bone Structure
Introduction
As people age, cortical bone becomes thinner and trabeculae are resorbed decreasing overall connectivity. In certain cases the rate of change is greater than normal, resulting in osteoporosis and possible fracture. Currently, osteoporosis is diagnosed using dual energy x-ray absorptiometry (DXA). These machines are expensive to acquire, maintain and use, they expose patients to ionising radiation and they are, in general, non-portable and only suitable for use by highly skilled professionals. Quantitative ultrasound (QUS) may offer a cheaper, simpler technique to assess skeletal condition. US has been shown to penetrate the finger via three separate pathways. The amount of energy coming from these pathways was seen to change depending on the cortical area. The aim of this study was to try to attempt to quantify the relationship between these.

Methods
pQCT scans were taken along the proximal phalanx of 14 volunteers (8F/6M) to determine the Cortical Area (CA), Cortical Density (CD) and the geometry of the phalanxes. The pQCT images were used to produce a voxel-based model to simulate the passage of an ultrasonic wave across the finger using Wave2000 software. The energies from the different wave components were established. These values were then compared to the actual cortical area present to see if they were significantly correlated.

Results
The challenging aspects of the technique were: setting the minimum time of flight and the noise threshold level (for triggering the data acquisition) and defining the window capturing data after the first wave ripples have arrived at the receiver. Once these have been established, the combined scanning and simulation routine we used here showed that measuring the energy of the early arriving signal and expressing this as a proportion of the total energy correlated well with cortical area.

Discussion & Conclusion
On the basis of these results, it may be possible to determine cortical area using QUS and this in turn may be used to deduce overall skeletal condition in an inexpensive and effective manner. Also, this technique may be used to monitor bone loss if used to gauge cortical thinning.

References
1 Barkmann et al, Osteoporos Int, 11:745-755, 2000
2 Cadossi et al, Osteoporos Int, 6:196-206, 1996